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THE DIGITAL VASCULAR SYSTEM

WITH REFERENCE TO THE STATE OF GLOMUS IN INFLAMMATION, ARTERIOSCLEROTIC GANGRENE, DIABETIC GANGRENE, THROMBOANGIITIS OBLITERANS AND SUPERNUMERARY DIGITS IN MAN

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In 1924 Masson [1a] published a paper on the subject of peculiar small subungual tumors, benign in structure and clinically manifested by much pain. He considered these tumors as being genetically related to peripheral arteriovenous anastomoses. Owing to their resemblance to the gland of Luschka, or the glomus coccygeum, Masson chose for these tumors the name glomic tumors.

Knowledge of the relation of glomic tumors to peripheral arteriovenous anastomoses involves consideration of present knowledge of the anatomy and physiology of these anastomoses. Sucquet [2] described peculiar vessels in several regions in the palm and sole, especially in the median zone on the ventral surface, which appeared to be larger than ordinary capillaries and which opened directly into the neighboring veins without forming a capillary network. In his studies Sucquet employed a method of injection, dissection and examination by a magnifying glass. To Hoyer [3] must be given the main credit for masterly anatomic studies on arteriovenous anastomoses. He used better methods than those of Sucquet, and his studies present a thorough anatomic and topographic description of arteriovenous anastomoses. The correctness of Sucquet-Hoyer's anatomic concept was corroborated later by histologic studies (Grosser,[4] Schumacher,[5] Masson,[1] Clara [6]

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1. Masson, P.: (*a*) Lyon chir. **21**:257, 1924; (*b*) Arch. per le sc. med. **50**:1, 1927.

2. Sucquet, quoted by Testut, I. L., and Testut, J.: Traité d'anatomie humaine, Paris, Gaston Doin & Cie, 1921, vol. 2, p. 101.

3. Hoyer, H.: Arch. f. mikr. Anat. **13**:603, 1887.

4. Grosser, O.: Arch. f. mikr. Anat. **60**:191, 1902.

5. Schumacher, S.: Arch. f. mikr. Anat. **87**:309, 1916.

6. Clara, M.: Ergebn. d. Anat. u. Entwcklngsgesch. **27**:246, 1927.

7. (*a*) Grant, R.: Heart **15**:281, 1931. (*b*) Grant R., and Bland, E.: ibid. **15**:385, 1931.

and others). Grant and Bland [7] were the first physiologists to study arteriovenous anastomoses with the use of modern physiologic methods. As to observations on the changes of arteriovenous anastomoses in pathologic conditions, nothing is found in the literature, with the exception of Masson's discussion of glomic tumors. Even Buerger's [8] fundamental clinical treatise on disorders of the vascular system fails to mention peripheral arteriovenous anastomoses and their possible relation to some of the peripheral vascular disturbances.

MATERIAL AND METHODS

Guided by the experience of the aforementioned authors, who studied arteriovenous anastomoses in various animals and in different parts of the body, I limited my investigations to the study of digital arteriovenous anastomoses in man. Cases of normal persons of different ages, including the human fetus of from 4½ months to term, were studied. My pathologic material covered the following conditions: digital cellulitis, arteriosclerotic gangrene, diabetic gangrene and thrombo-angiitis obliterans. I also had an exceptional opportunity to examine slides from Cummins' [9] work on spontaneous amputation of supernumerary digits (pedunculated postminimi) in man.

Almost all the previous investigators who studied the arteriovenous anastomoses employed the method of intravascular injections with coloring substances. My investigations were done with fresh surgical material fixed in situ, without being subjected to intravascular injections of fixing fluids and coloring substances. Picroformol of Bouin [9a] was employed as the principal fixative. In each case the pieces for embedding in paraffin were taken from the following regions: the pad (ventral surface), both lateral surfaces, the nail bed and the nail matrix. The methods of staining employed were: Masson's trichrome stain,[9b] Weigert and

8. Buerger, L.: The Circulatory Disturbances of the Extremities, Philadelphia, W. B. Saunders Company, 1924.

9. Cummins, H.: Am. J. Anat. **51**:381, 1932.

9a. The formula for picroformol of Bouin is as follows: formaldehyde solution, 10 per cent; water, 30 per cent, and glacial acetic acid, 2 per cent, with trinitrophenol added to saturation.

9b. Masson's trichrome stain is composed of iron, hematoxylin, fuchsin, Poinceau de xylidine (an azo dye of the aminobenzidine sulphonatronic acid group) and aniline blue. The procedure of this method is as follows: Mordant sections are immersed in iron and aluminum at 40 C. for five minutes and in iron and hematoxylin at 40 C. for five minutes. This is followed by stirring in a jar of 95 per cent alcohol for a few minutes and by differentiation in picric alcohol. The sections are then washed in running water for fifteen minutes, stained with Poinceau-fuchsin solution (fuchsin acid, 1:100, one part, and Poinceau de xylidine, 1:100, two parts) for five minutes and rinsed in distilled water. They are then immersed in phosphomolybdic acid for five minutes and rinsed again in distilled water. About 10 drops of aniline blue is put on the slide for from ten to fifteen minutes, and the sections are placed in phosphomolybdic acid for five minutes and then in acetic acid solution, 1:50 or 1 per cent, for from two to three minutes. This is followed by dehydration with absolute alcohol and clearing in toluene. The sections are mounted in balsam to which 0.5 per cent of dry powdered salicylic acid is added.

Duval's stain for elastin, Mallory's stains for fibrin and silver impregnation methods of Rogers,[9c] Foot [9d] and Schultze-Stohr.[9e]

Digital arteriovenous anastomoses are situated in the deeper layer of the corium or in the stratum reticulare. There they occupy a narrow zone which lies parallel to the surface of the skin. For this topographic reason all the blocks of my normal and pathologic material were sectioned parallel to the surface of the skin. Such orientation permits examination of the various zones of the skin in their topographic sequence. For making quantitative studies and for measuring the individual arteriovenous anastomoses, the advantage of this method is obvious. The observations reported here are based chiefly on the method of reconstruction from serial sections.

NORMAL DIGITAL ARTERIOVENOUS ANASTOMOSES OF THE SUCQUET-HOYER TYPE

Before presenting my observations in cases of normal adults and fetuses, it is appropriate to summarize the essentials concerning the present knowledge of the anatomy and histology of normal digital arteriovenous anastomoses of the Sucquet-Hoyer type. As a general rule, the arteriovenous anastomoses are seen almost exclusively over the ventral surface of the hand and foot. They are constantly present in the region of the nail bed and in the tips of the digits, the palmar surfaces of the first, second and third phalanges and the thenar and hypothenar eminences of the hand. Arteriovenous anastomoses in the foot are distributed in a way similar to those of the hand. Besides being seen in the nail bed and the lateral surfaces and pads of the

9c. The method of Rogers consists in fixation in from 10 to 20 per cent formaldehyde or Bouin's picro-aceto-formaldehyde, embedding in paraffin, the cutting of sections impregnated with 40 per cent silver nitrate solution, reducing with di-ammoniacal solution toning with gold chloride solution, and fixing in 5 per cent sodium hyposulphite. The specimens are then washed, dehydrated and mounted.

9d. The method of Foot is as follows: fixation in Carnoy's solution (absolute alcohol, six parts; chloroform, three parts, and glacial acetic acid, one part); embedding in paraffin; pretreatment with a mixture of pyridine, two parts, and glycerol, one part; washing with 95 per cent alcohol; washing with distilled water; impregnation with 10 per cent aqueous silver nitrate at 37 C.; development for twenty minutes in 5 per cent neutral formaldehyde solution; developing with 0.5 per cent pyrogallol; washing; toning with gold chloride solution; intensifying by means of immersion for five minutes in oxalic acid; fixing for five minutes in 5 per cent aqueous solution of sodium thiosulphate; washing at the tap; dehydrating; running through xylene, and mounting in Canadian balsam.

9e. Variation 9 of the method of Schultze-Stohr for staining peripheral nerves consists in: fixation in 10 per cent formaldehyde; the making of a frozen section; immersion in 10 per cent sodium hydroxide for twenty-four hours; washing with distilled water for from one to two hours, with from four to six changes; immersion in silver nitrate, 10 per cent, for twenty-four hours; reduction with hydrochinon formaldehyde; dehydration, and mounting.

toes, they are found in the sole near the heel. Being formed by branches of preterminal subcutaneous arteries, the zone of the arteriovenous anastomoses is located a little deeper than the web of subpapillary arteries and veins. The topographic relation of subcutaneous arteries to branches which form arteriovenous anastomoses shows considerable variation. The main type of anastomosis is usually seen in the pulp of the finger and is formed as follows: The afferent artery arises from branches which run in subcutaneous tissue parallel to the surface of the skin. These large branches go upward and toward the surface. After they reach the inner zone of the stratum reticulare, each divides into two branches. The stronger branch bends at a right angle and continues parallel to the skin, and the weaker branch divides again. Some of the divisions of the weaker branch contribute to the formation of arteriovenous anastomoses; some go to the papillary bodies, and the artery itself ends as an artery of the papillary body. The arterial branches which become transformed into arteriovenous anastomoses acquire a peculiar appearance, owing to specific changes in their walls. The anastomosis is S-like in appearance, twisting, coiling and seldom straight. The lumen is narrow and irregular. Its endothelial cells are voluminous and cuboidal and are arranged in two or three rows; their nuclei stain deeply. There is no internal elastic lamina. The muscular coat is characterized by the presence of inner longitudinal and outer circular layers. These layers are indistinct. Amid the muscle cells are seen large, clear, epithelioid-like cells with oval or globular nuclei which are poor in chromatin. The cytoplasm of these cells is either clear or vacuolar and shows no particular tinctorial affinity. It is poor in myofibrils and gives no reaction for glycogen, fat or mucin (Schumacher [5]). Ramifying among these cells are seen anastomosing cells with elongated nuclei and transparent cytoplasm without myofibrils (Masson [1b]). The outer zone of the arteriovenous anastomosis consists of loose delicate collagenous reticulum, in the meshes of which are seen numerous nonmedullated nerves. These fibrils are demonstrable with methods of staining with methylene blue (Grant [7a]) and with Cajal's method of retaining with silver (Alvarez and Costero [10]). The entire arteriovenous anastomosis is surrounded by coarse, lamellated collagenous tissue, in the meshes of which are found collecting veins. The primary collecting veins into which the anastomoses drain are characterized by a thin wall almost devoid of muscular cells. These veins surround arteriovenous anastomoses in the form of plexuses. Primary collecting veins open into subpapillary veins and, through the latter, into deeper veins. Quantitative studies of arteriovenous anastomoses give figures

10. Alvarez, C., and Costero, I.: Arch. españ. de oncología **2**:391, 1931.

which differ considerably. Grant and Bland's [7b] figures in square centimeters for the index finger are as follows:

Nail bed	501
Tip	236
Palmar surface of third phalanx	150
Palmar surface of second phalanx	20
Palmar surface of the first phalanx	93
Thenar eminence	113
Hypothenar eminence	96

Their figures for the foot (second toe) are:

Nail bed	593
Pad	293
Sole near heel	197

As to the size of the individual anastomoses, the following figures in microns for the nail bed are given by Grosser: [4]

Outer transversal region	55-65
Inner transversal region	18-22

For the finger pulp the figures are:

Outer transversal region	90-150
Inner transversal region	10-30

The optical section of the arterial portion is narrower than that of the venous portion. From the data reviewed it is evident that arteriovenous anastomoses must be considered as a peculiar peripheral neurovascular anatomic unit of complicated structure and important function.

PERSONAL OBSERVATIONS

The serial method employed in my studies not only permitted complete examination and reconstruction of individual arteriovenous anastomoses, but also gave an opportunity to study the entire topographic relation of anastomoses to the surrounding structures. In my description I have adopted the following nomenclature: The portion of the channel connecting artery and vein, or the arteriovenous anastomosis proper, I call the Sucquet-Hoyer canal. The entire anastomotic unit, which includes (1) the afferent artery, (2) the Sucquet-Hoyer canal, (3) the neuroreticular and vascular structures around the Sucquet-Hoyer canal, (4) the outer lamellated collagenous tissue and (5) the primary collecting veins, I call the glomus.

In the first serial sections the periphery of the glomus starts as a round, light area consisting of loose collagenous reticulum and surrounded by coarse, lamellated collagenous tissue. This area is supplied with capillaries, which, for the most part, are cut longitudinally. The

capillaries drain into small slitlike veins, which are located in the meshes of coarse collagenous tissue. Some of these capillaries are twisted around and run along the smaller and larger nerve trunks which are always found at the periphery of the glomus. As soon as the first muscular cells of the Sucquet-Hoyer canal begin to appear, the capillaries become less numerous and less conspicuous. Their endothelial cells intermingle with muscle cells, and only by their large size and deep staining can they be differentiated from the latter. The muscle cells which appear first are elongated, have fusiform nuclei and are circular in arrangement. On reaching the lumen of the Sucquet-Hoyer canal and in the sections cut transversely, the inner muscle cells are arranged more or less longitudinally, while the outer muscle cells are arranged in circular fashion. No true separate longitudinal and circular muscle layers are found in the walls of the Sucquet-Hoyer canal. Depending on orientation, the state of contraction or relaxation and the level of sectioning, the nuclei of individual muscle cells may appear different in size and shape. These factors also determine the appearance of the cytoplasm in the individual muscle cells. Most of the minute tubular and ringlike structures which are seen in the walls of the Sucquet-Hoyer canal are cytoplasmic extensions of muscle cells cut longitudinally and transversely. Amid the ordinary muscle cells are found large epithelioid cells with clear cytoplasm and round or globular nuclei. Followed in serial sections, these epithelioid-like cells appear to be transversely cut muscle cells with voluminous cytoplasm and slightly elongated polyhedral nuclei.

The entire muscular coat of the Sucquet-Hoyer canal is surrounded with a wide clear zone consisting of delicate collagenous reticulum and containing numerous nonmedullated nerves. With fresh and well fixed material, the trichrome staining of Masson is most helpful for studies of this neuroreticular clear zone and of the smaller and larger nerve trunks always seen in the outer glomic zone. Because it is uniformly constant and selective in its tinctorial affinity, trichrome staining permits detailed topographic studies in serial sections, and the latter compensates for failure of this staining to disclose nerve endings and neurofibrils.

The silver impregnation methods of Rogers, Foot and Schultze-Stohr, when applied to the cutaneous digital glomus, failed to give constant results in my studies. The Schultze-Stohr silver method, however, gave more reliable and selective impregnation. With the silver impregnation a rich network of neurofibrils in close proximity to the muscular walls of the Sucquet-Hoyer canal is seen. No particular or structurally specific nerve endings are found. On the whole, the results with silver impregnation of the skin of the digits are too inconstant to permit proper deductions. Because of their netlike, interlaced arrangement, unmyelinated nerve fibers of the clear periglomic zone appear in

trichrome-stained sections as homogeneous, structureless tubules and rings from 0.5 to 1.5 microns in thickness. These structures are more numerous around the proximal and middle parts of the Sucquet-Hoyer canal, but are inconspicuous in the distal portions. Almost invariably the neurotubular network, if followed in serial sections, is seen to be connected with very small nerve trunks, which in turn can be followed to the point of their connection with large periglomic nerve trunks. Along the course of these minute tubules and rings are seen small, deeply stained, round and rodlike nuclei of Schwann's sheaths. These nuclei become more numerous on approaching the larger nerve trunks.

The intermuscular reticulum is almost invisible. No true internal or external elastic tunica is found. Near the afferent portion of the Sucquet-Hoyer canal the muscular wall becomes narrower and more compact. At the point where the Sucquet-Hoyer canal begins there is a distinct collagenous ruffle containing an elastic lamina (fig. 1) under the endothelium. This structure must be of physiologic significance, and it is at this point that certain pathologic changes of the Sucquet-Hoyer canal are first observed. The lumen of the main afferent artery, if cut transversely and just behind this point, is irregular and corrugated and shows cushion-like elevations consisting of an elevated intima with a bud of longitudinal muscles underneath. The region of the afferent artery where these endotheliomuscular elevations are seen corresponds topographically to the place of the beginning of from two to five small arterioles. These arterioles always begin proximally to the Sucquet-Hoyer canal. Their capillaries supply the walls of the Sucquet-Hoyer canal, the clear neuroreticular zone around this canal and the nerve trunks of the periglomic zone. In other words, they supply all the constituents of the glomus. I call these arterioles preglomic arterioles. Thus, the cushion-like endotheliomuscular elevations in the afferent artery correspond to the place where the Sucquet-Hoyer canal and the preglomic arterioles begin. Their function is to direct the flow of blood into the Sucquet-Hoyer canal and preglomic arterioles. The proximal parts of preglomic arterioles often travel for some distance in the wall of the Sucquet-Hoyer canal. In such cases preglomic intramural arterioles differ from the Sucquet-Hoyer canal with respect to their narrow round lumen, the presence of an internal elastic lamina and their narrow compact layer of circularly arranged muscle cells. Preglomic arterioles are sometimes situated in the vicinity of the Sucquet-Hoyer canal and may be taken for part of this canal, if examined in a single section. Twistings and angulations of the Sucquet-Hoyer canal create the impression that it divides or breaks into several branches. From serial sections it is evident that the passage of this canal is usually single and that preglomic arterioles at no place communicate with its lumen. Sometimes, however, division of the efferent part of the canal into two or three branches is observed.

Explanation of Plate I

Fig. 1.—Section of the glomus at the point where Sucquet-Hoyer's canal begins. An afferent artery is shown below; in the center is the glomus, with the proximal part of the Sucquet-Hoyer canal furnished with elastic lamina, and in the upper part is a section of the primary collecting vein, with its outer wall richly supplied with elastic fibrils. Weigert's elastin stain; camera lucida drawing; ocul., 2 ×; obj., 9 ×.

Fig. 2.—The efferent part of the Sucquet-Hoyer canal, with part of the primary collecting vein showing only a few muscular cells and with a clear neuroreticular zone present only around the canal. Masson's trichrome stain; camera lucida drawing; ocul., 2 ×; obj., 9 ×.

Fig. 3.—The glomus in diabetic gangrene, with hyalinization of the Sucquet-Hoyer canal, which is cut at various levels. The preglomic arterioles, seen on the left side of the glomus, are markedly thickened, hyalinized and dilated. The periglomic, clear neuroreticular zone is replaced with thick bundles of collagenous tissue. The primary collecting vein appears as a long, wide cleft encircling the glomus from the right side. The secondary collecting vein is seen in the lower right corner; it is cut transversely and is widely dilated. Masson's trichrome staining; camera lucida drawing; ocul., 10 ×; obj., 16 ×.

Fig. 4.—The glomus in arteriosclerotic gangrene, with hyalinization of the afferent artery, thickening, distortion and breaking of the elastic fibrils and consequent collapse and permanent dilatation of the Sucquet-Hoyer canal. The periglomic area shows massive sclerosis. Camera lucida drawing; ocul., 10 ×; obj., 16 ×. Figure 18 shows same field under lower magnification.

Fig. 5.—Camera lucida drawing made from section 13 of figure 23 and illustrating the relation of digital arteriovenous anastomoses in thrombo-angiitis obliterans. It shows: a small valvular vein (*V*1) in the upper right corner; second vein (*V*2) in the upper left corner (*V*2 shows a distinctly visible valve at its top); another vein (*V*3) at the bottom; the anastomosing artery *A*1 approaching the vein (*V*3) formed by the union of the two veins mentioned (*V*1 and *V*2) from below on the right side and a second anastomosing artery (*A*2) approaching the vein *V*3 from below on the left side. The anastomosing arteries *A*1 and *A*2 show fusiform dilatation. Masson's trichrome stain; ocul., 5 ×; obj., 16 ×.

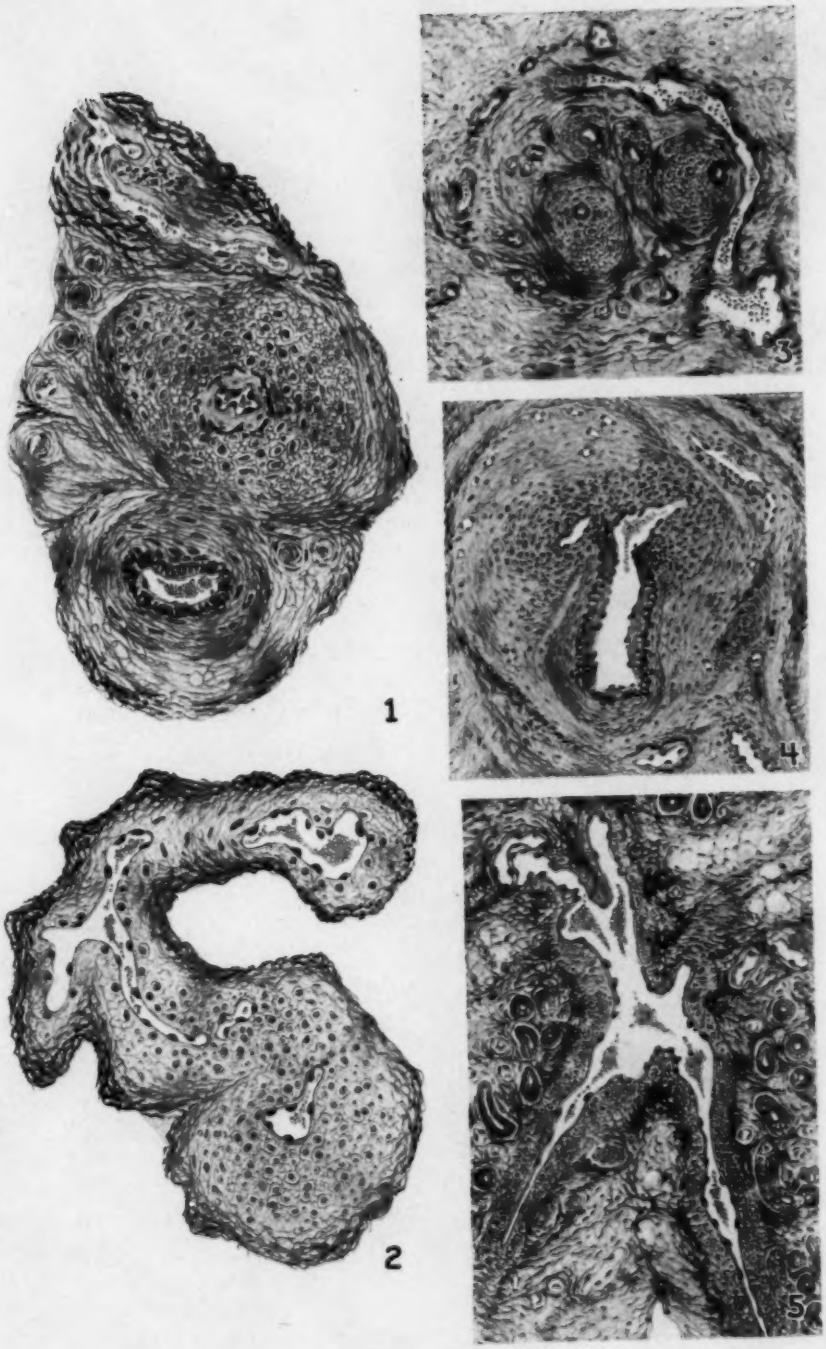


Plate 1

Photomicrographs 6 to 13 were taken from serial sections. The corresponding numbers of these serial sections are 45, 44, 43, 42, 40, 38, 35 and 30. Figure 6 shows the place of the cushion-like endotheliomuscular elevations in the afferent artery, which is seen in the center of the field. The arterial lumen is single, but irregular and corrugated. Figures 7 and 8 demonstrate the formation of two separate lumens—one (on the right) of a Sucquet-Hoyer canal and the other (on the left) of a preglomic arteriole. Figures 9, 10 and 11 show the small round lumen of a preglomic arteriole in the upper left quadrant. The preglomic arteriole runs independently in the wall of the Sucquet-Hoyer canal, and the canal follows its own way. In figure 12 the muscle cells of the Sucquet-Hoyer canal begin to disappear, while the lumen of a preglomic arteriole is still seen in the same quadrant. In figure 13 the muscle cells of the Sucquet-Hoyer canal disappear entirely, and the preglomic arteriole divides into several capillaries, which supply the entire glomic unit and the periglomic nerve trunks. (One of the nerve trunks with a capillary is seen in the lower quadrant of the glomus a little to the left.) Figure 14 demonstrates a coiled Sucquet-Hoyer canal cut at different levels. The afferent artery is seen in slightly oblique sectioning. The efferent part of the canal is shown in the upper left corner as an irregular opening with a thin wall. One of the preglomic arterioles is cut longitudinally and is directed toward the periglomic nerve trunk. Several capillary openings of preglomic arterioles are seen in the periglomic zone.

The efferent, or venous, part of the Sucquet-Hoyer canal is characterized by a thin wall with a few muscular cells, by disappearance of a clear neuroreticular zone and by an abundance of elastic tissue in its outer coat (fig. 2). The efferent part of the canal and the capillaries of preglomic arterioles enter the same collecting vein. The width of the primary collecting vein, when empty, is almost that of an ordinary capillary (from 8 to 15 microns). If cut longitudinally, it appears like a capillary slit from 200 to 300 microns in length. It can be differentiated from the capillary only by examination in serial sections. The vascular slit of a longitudinally cut vein can be followed in 15 consecutive sections 7 microns in thickness. Only 1 or 2 sections 7 microns thick are necessary to cover the longitudinally cut capillary. On reconstruction from the serial sections, it was seen that the collecting vein has the shape of a broad ruffle or cape, which encircles the glomus and forms a voluminous receptaculum with a highly developed surface area. In figure 7 such orientation of the primary collecting vein is shown conspicuously, and the vein appears as a long perpendicular slit on the left side of the glomus. This venous slit appears in figures 6 to 12, but is shown best in figure 7. Primary collecting veins are richly supplied with elastic tissue, but they are poor in muscle cells. These veins open

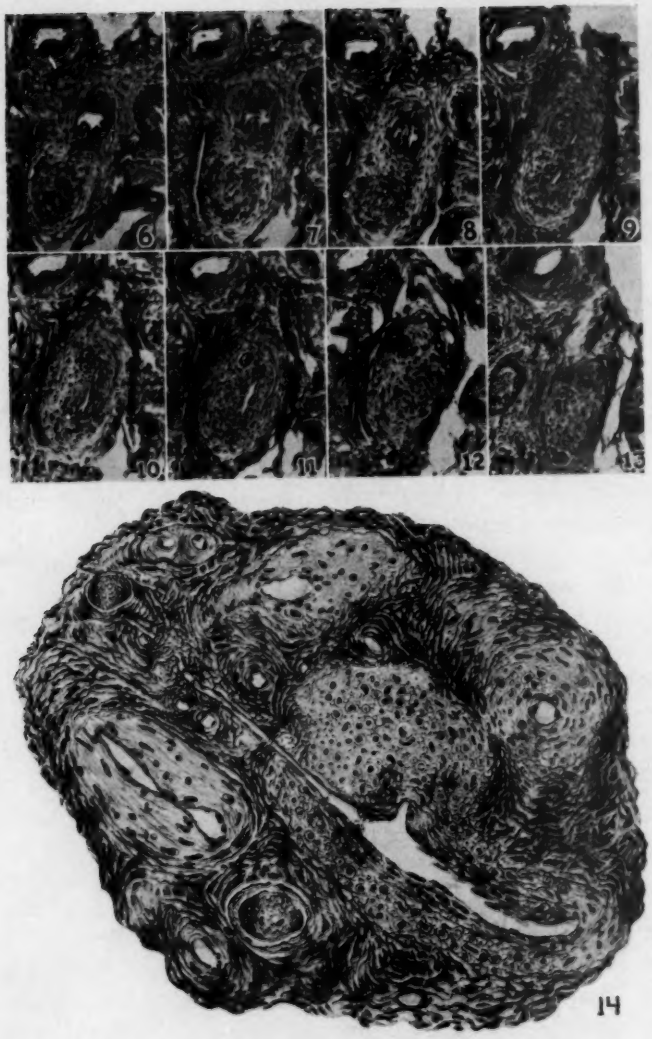


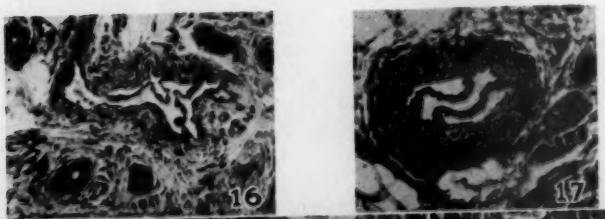
Plate 2

EXPLANATION OF PLATE 2

Figs. 6 to 13.—Photomicrographs from corresponding serial sections 45, 44, 43, 42, 40, 38, 35 and 30. Figure 6 shows the afferent artery (in the center), its lumen being irregular on account of endotheliomuscular elevations. Figures 7 and 8 show separation of two lumens, the one on the right of the Sucquet-Hoyer canal and the one on the left of the preglomic arteriole. In figures 9, 10 and 11 an intramural preglomic arteriole is seen in the upper left quadrant, while the Sucquet-Hoyer canal follows its own way. Figure 12 shows the periphery of the glomus; only a few muscular cells are seen. In figure 13 the muscle cells of the Sucquet-Hoyer canal have disappeared entirely, and the preglomic arteriole breaks into capillaries supplying all the constituents of the glomus, including preglomic nerve trunks. One of the nerve trunks is seen in the lower pole of the glomus, and the capillary approaching it is shown. The primary collecting vein is located on the left side of the glomus. It is best seen in figure 7 and appears as a perpendicular slit encircling the glomus from the left side. This venous slit is seen in consecutive serial sections 45 to 35. Masson's trichrome stain; ocul., 10 ×; obj., 16 ×.

Fig. 14.—A coiled Sucquet-Hoyer canal cut at different levels. The afferent artery is below on the right in slightly oblique sectioning. The proximal part of the canal is shown in the center, with a clear periglomic neuroreticular zone. The with opening of the efferent part of the canal is in the upper middle quadrant. One of the preglomic arterioles, cut longitudinally, is directed toward the nerve trunk, shown in the upper left quadrant. Several small capillary openings of the preglomic arterioles, supplying all the constituents of the glomus, are shown. Masson's trichrome stain; camera lucida drawing; ocul., 2 ×; obj., 9 ×.

STRATUM PAPILLARE
STRATUM RETICULARE
STRATUM SUBCUTANEUM
15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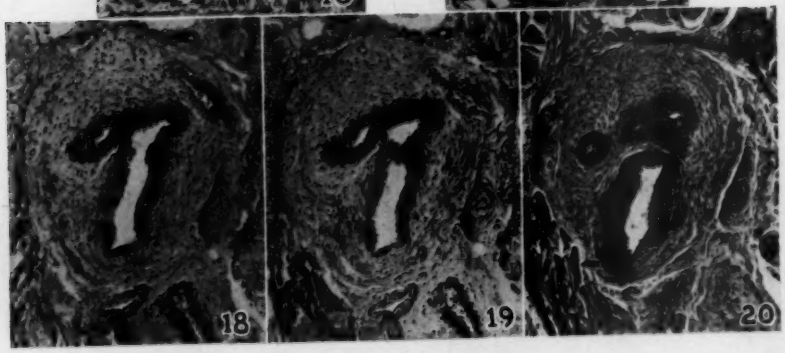

18
19
20

Plate 3

EXPLANATION OF PLATE 3

Fig. 15.—Diagrammatic presentation of vascular arrangement and the glomus, as found in the ventral surface of the digit. It shows: (1) all the zones of the skin, including that occupied by the glomic apparatus; (2) the afferent artery of the glomus; (3) the coiled type of Sucquet-Hoyer canal, characterized by a thick wall; (4) the efferent part of the Sucquet-Hoyer canal entering the primary collecting vein, with the latter appearing as a long, wide ruffle encircling the glomus; (5) the relation of the primary collecting vein to other veins; (6) the system of preglomic arterioles supplying all the constituents of the glomus and emptying into the primary collecting vein, and (7) division of the periarterial nerve trunks, with branches going to the glomus. This diagram serves to explain arteriovenous and trophic disturbances caused by functional disability and organic destruction of either the entire glomus or one of its constituents.

Fig. 16.—Photomicrograph showing vein of amuscular type of the stratum reticulare, measuring 60 by 120 microns, with 2 valves of the ostial type. Ocul., 10 ×; obj., 16 ×.

Fig. 17.—Muscular type of vein of the stratum subcutaneum, measuring 240 by 400 microns, with two parietal valves supplied with elastic fibrils. Masson's trichrome stain controlled for elastin; ocul., 7.5 ×; obj., 16 ×.

Figs. 18, 19 and 20.—Photomicrographs of corresponding serial sections 22, 21 and 16. These three figures demonstrate the proximal part of the digital glomus as found in senile arteriosclerosis. The afferent glomic artery is sclerosed and shows none of the endotheliomuscular elevations normally seen, which are demonstrated in figure 6. The proximal part of the Sucquet-Hoyer canal is wide open (fig. 18). The periglomic, clear neuroreticular zone is replaced with dense collagenous tissue. The periglomic nerve trunks seen on the left, and especially on the right, side of the glomus, show massive lamellated fibrosis. Figures 18 and 19 show sections stained with Weigert's method for elastin. Figure 20 shows a section stained with Masson's trichrome method. Ocul., 7.5 ×; obj., 16 ×. Figure 18 should be compared with figure 4, which shows the same field under higher magnification.

into subpapillary veins and thence into deep veins. The collecting veins of the stratum reticulare and stratum subcutaneum are furnished with valves. The statement made in a standard book of anatomy that the smaller veins, i. e., those less than 2 mm. in diameter, have no valves is incorrect. Even very small peripheral digital veins show the presence of valves. Figure 16 shows a vein in the inner zone of the stratum reticulare, with two distinctly visible valves of the ostial type. This particular vein measures 60 by 120 microns. Its wall is thin and practically devoid of muscle cells. The valves of the peripheral digital veins are mainly of the ostial type. In smaller veins they consist of delicate connective tissue membrane lined on both sides with endothelial cells. The valves of the large veins have, in addition, fine subendothelial elastic fibrils. Elastic fibrils are better differentiated on the inner surface of the valves than on the outer surface facing the valvular sinus. Figure 17 shows a larger vein of the stratum subcutaneum with a valve of the parietal type, the latter being supplied with elastic fibrils.

Figure 15 recapitulates diagrammatically the anatomic observations described. It shows all zones of the skin, including the zone occupied by glomic formations. The entire arteriovenous system of the ventral surface of the digit is presented topographically. The relation of the Sucquet-Hoyer canal to the afferent artery and the preglomic arterioles is indicated. The primary collecting vein of the glomus and its relation to the peripheral and deeper veins are shown. The distribution of the periglomic nerves and their relation to the capillaries of the preglomic arterioles are seen.

My studies on the quantitative distribution of the Sucquet-Hoyer canal covered the terminal (ungual) phalanx of the hand and foot. Countings were made from the following regions: the ventral surface, both lateral surfaces, the nail bed and the nail matrix. The digital glomus presents an unstable anatomic unit, and the quantitative results are influenced by a number of factors, of which the age of the person and the pathologic processes are the most important. Examination of the digital vascular system in fetuses from the age of 4½ months to term disclosed complete absence of the Sucquet-Hoyer canal. While sweat glands, nerve trunks and tactile bodies appeared well developed, no formation similar to the Sucquet-Hoyer canal of normal adults was found. In persons over 60 years of age the number of digital Sucquet-Hoyer canals per square centimeter begins to decrease, and this decrease progresses with advance in age. An estimate of the average number of these canals per square centimeter of surface area in the big toe of a normal person 20 years old gives the following figures: ventral surface, 18; lateral surface, 10; nail bed, 24, and nail matrix, 12. The figures obtained from corresponding parts of the thumb are approximately the same. These figures are strikingly lower

than those of Grant and Bland [7b] which have already been cited. My calculations are based on the examination of each individual glomus, not as it appears in a single section, but as it is followed from the beginning to the end in serial sections. I took for arteriovenous anastomoses or for true Sucquet-Hoyer anastomoses only the anatomic structures which were formed in accordance with the descriptions of Sucquet, Hoyer and Grosser. Unmolested by intravascular injections under pressure of washing, fixing and coloring fluids, my fresh surgical material, fixed *in situ,* revealed the state of the vascular digital system as it existed at the time of fixation. Though laborious, my method gives an accurate idea as to the appearance of the glomus at different levels of sectioning. With this method the chance of recounting Sucquet-Hoyer canals is removed, and mistaking anastomoses for short preglomic arterioles, which run in close proximity to the canals and drain into the same collecting vein, is avoided. The figures of Grant and Bland [7b] were obtained with the method of intravascular injection of washing, fixing and coloring fluids. Their countings were made on cadavers within twenty-four hours after death.

In measuring individual Sucquet-Hoyer canals, I considered a clear periglomic zone as an integral part of a normal glomus. My figures are: pad of the toe, from 120 to 220 microns, and nail bed, from 60 to 150 microns. The distance from the inner surface of the epidermis to the outer portion of the glomus in digits of average size and development measured from 0.5 to 1 mm. No particular relation of the glomus to the pacinian corpuscles was observed.

From anatomic studies it appears that the digital glomus is a unit of specific structure. The essential characteristics of the Sucquet-Hoyer canal and the entire digital glomus may be summarized as follows:

1. The glomic system occupies a definite zone in the cutis.

2. One afferent glomic artery forms from one to four separate Sucquet-Hoyer canals.

3. The beginning of the Sucquet-Hoyer canal is marked by the presence in the afferent artery of cushion-like endotheliomuscular elevations, the function of which is to direct the blood flow into the Sucquet-Hoyer canals and preglomic arterioles.

4. The wall of the Sucquet-Hoyer canal is rather thick and has a specifically arranged structure.

5. The Sucquet-Hoyer canal is free from elastic tissue, with the exception of its proximal part.

6. The Sucquet-Hoyer canal is surrounded with a clear, wide zone consisting of loose, fine collagenous reticulum enclosing a rich network of nonmedullated nerve fibrils. This clear zone may be considered as

an expansion zone which is furnished with a neuroreticular mechanism controlling the function of the Sucquet-Hoyer canal.

7. The glomic unit is supplied with a specifically arranged system of preglomic arterioles, which nourish all the constituents of the glomus and form an integral part of a functional glomic unit.

8. Primary collecting veins, though lacking in musculature, are richly supplied with elastic tissue. They collect blood not only from the Sucquet-Hoyer canal but also from the preglomic arterioles. Being long and wide, they encircle the glomic unit and thus form a voluminous receptaculum, which has a highly developed surface area.

9. The entire glomus is surrounded with coarse, lamellated collagenous tissue, which separates the glomus from other structures of the cutis.

For proper understanding of the physiology and pathology of the digital glomus, each integral part of it must be taken into consideration.

THE GLOMUS IN PATHOLOGIC CONDITIONS

Inflammation.—Digits with nonspecific cellulitis from otherwise normal persons were examined. In the early stage of inflammation there are seen in the cutis numerous large, well circumscribed foci of lymphoid infiltration. These foci correspond topographically to the seat of the glomus. They consist of engorged capillaries of preglomic arterioles filled with numerous lymphocytes and polymorphonuclear leukocytes. Massive emigration of these cells through the walls of these capillaries is seen. Following this, both the clear periglomic zone and the muscular wall of the Sucquet-Hoyer canal are infiltrated with inflammatory elements. Muscular cells, especially those of epithelioid type, undergo pyknotic change and begin to decrease in number. No phagocytosis of muscular cells and, owing evidently to the absence of elastic tissue, no formation of foreign body giant cells are noted. The muscular cells simply move to the periphery and lodge in the spaces between the bundles of connective tissue. In the stage of advanced inflammation the wall of the Sucquet-Hoyer canal appears denuded, and its lumen is wide open. Capillaries of preglomic arterioles and the primary collecting veins are distended with stagnant blood. Anatomic changes, caused by inflammation, lead to functional collapse of the glomus. If not completely destroyed, glomic units regain their normal appearance. When damage is irreparable, obliteration of the glomus takes place. In case of local obliteration of the Sucquet-Hoyer canal, a new arteriovenous anastomosis anatomically similar to the original one can be formed. A new Sucquet-Hoyer canal develops from one of the preglomic arterioles. The anatomic factors which favor the development of new canals from preglomic arterioles are: (1) Preglomic arterioles are located in proximity to the clear neuroreticular zone; (2) they are in intimate contact with both the smaller and the larger periglomic nerve trunks, and (3) they are short and open into the same vein which collects the blood from the Sucquet-Hoyer canal. This collecting vein presents a voluminous receptaculum of particular structure and differs in its topographic arrangement from other peripheral veins.

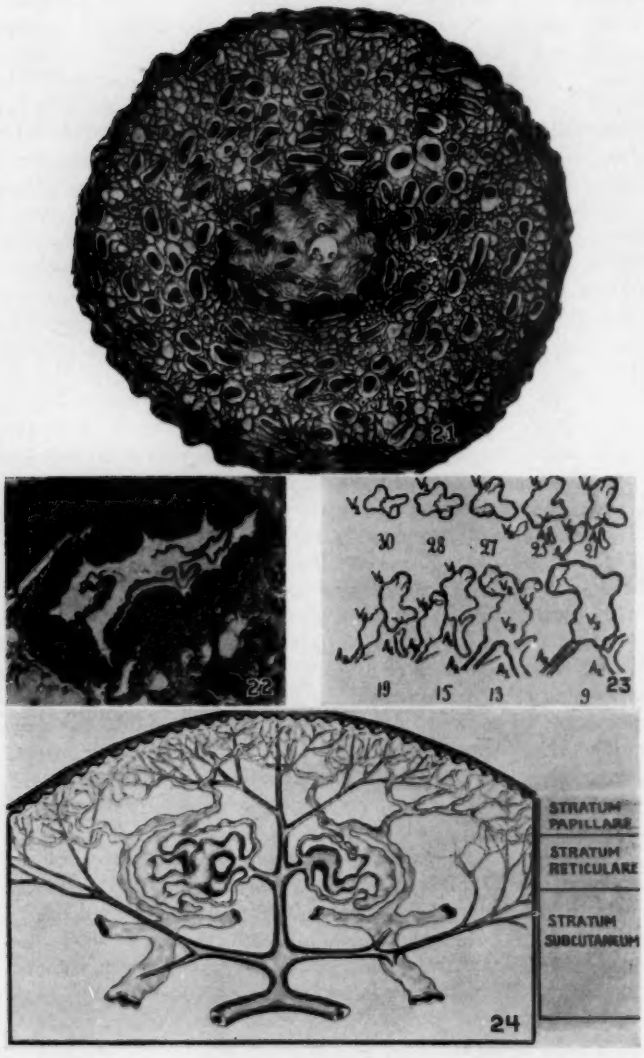
The observations in inflammation indicate that the glomic system is liable to qualitative and quantitative changes. Regressive changes do not necessarily lead to destruction of the Sucquet-Hoyer canals involved. Regeneration of these canals and even formation of new canals can take place.

Senile Arteriosclerotic Gangrene of the Foot.—Twenty-four patients were examined, the ages ranging from 60 to 81 years. In this condition general atrophy of the skin and cutaneous appendages is apparent. Of all the structures of the skin, the sweat glands are preserved best. No normal glomic units are observed, and the number of Sucquet-Hoyer canals per square centimeter is greatly reduced. While the average number of Sucquet-Hoyer canals in the tip of the toe of a normal person from 20 to 30 years of age is from 18 to 25 per square centimeter, in the person with senile arteriosclerotic gangrene only from 4 to 6 canals are found for 1 sq. cm. of the corresponding region. Pathologic changes of the Sucquet-Hoyer canals are due mainly to sclerotic thickening of the afferent arteries. The lumens of these arteries show no more cushion-like endotheliomuscular elevations, such as are normally seen at the place where the canals and preglomic arteries begin. Subendothelial hyalinization, distortion of the elastic lamina and increase in intermuscular collagenous tissue are prominent changes. It is these changes in the afferent artery that initiate the functional disability of the proximal part of the Sucquet-Hoyer canal. Later, preglomic arterioles undergo hyalinization, and as a result of this the clear neuroreticular periglomic zone is replaced with coarse collagenous tissue. Nerve trunks of the periglomic zone appear surrounded with lamellated, dense fibrous tissue.

Figures 18, 19 and 20, with corresponding serial numbers 22, 21 and 16, demonstrate changes of the Sucquet-Hoyer canal in senile arteriosclerosis, as described. If examined alone and in material poorly fixed and stained with hematoxylin eosin, figure 19 may create the impression that the lumen of the artery is divided into different compartments by bundles of connective tissue. Figure 20 of this series, however, indicates that figure 19 represents the proximal part of the Sucquet-Hoyer canal, which is altered on account of sclerosis of the afferent artery and fibrosis of the periglomic zone. In advanced cases the proximal portion of the Sucquet-Hoyer canal appears sclerotic; the elastic fibers are thickened, broken and distorted, and the entire canal is transformed into a functionally uncontrollable, wide open channel (figs. 4 and 18) through which arterial blood pours continuously into collecting veins. This, in turn, leads to upset of venous drainage in the entire region corresponding to the Sucquet-Hoyer canal involved. In efforts to adjust themselves to the altered mechanical conditions, all the veins of the corresponding region undergo muscular hypertrophy, with secondary dilatation. If sclerosis of the periglomic zone is predominant, the Sucquet-Hoyer canal undergoes obliteration and is replaced with hyalinized fibrous tissue. The valves of the hypertrophied deeper veins are thickened and hyalinized, the elastic fibrils being distorted (fig. 22). These valvular changes add to the disturbances of the venous drainage in the area impaired. The epidermal lining over the region involved shows marked hyperkeratosis. Chronic venous stasis leads to fibrosis and atrophy of the cutaneous appendages. Poorly nourished and diseased areas are predisposed to secondary inflammation, which contributes to more rapid deterioration of the glomic system.

Diabetic Gangrene of the Foot.—Nineteen patients with diabetic gangrene were examined. The majority of the cases were complicated by either secondary inflammation or arteriosclerosis, and for these reasons the changes of the glomus demonstrated all possible variants.

Examination of digits free from secondary inflammation and arteriosclerosis showed that in diabetic gangrene the glomus undergoes rather specific changes. In early cases, in which the afferent arteries are not much altered and in which primary collecting veins still hold their size and shape, the primary change is observed in the proximal part of the Sucquet-Hoyer canal, at the place where normally (fig. 1) a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STRATUM PAPILLARE
STRATUM RETICULARE
STRATUM SUBCUTANEUM
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Plate 4

EXPLANATION OF PLATE 4

Fig. 21.—Proximal part of the Sucquet-Hoyer canal in diabetic gangrene. The subendothelial collagenous ring, which is normal in the center of figure 1, appears thickened and hyalinized; the elastic fibrils are broken; the intermuscular collagenic tissue is increased; the periglomic neuroreticular zone is invaded with sprouts of collagenous tissue, and the outer periglomic zone shows massive lamellated fibrosis. Masson's trichrome stain; camera lucida drawing; ocul., 2 ×; obj., 2 ×.

Fig. 22.—Valvular insufficiency in a dilated and hypertrophied vein of the stratum subcutaneum from a patient with senile arteriosclerosis. The valves appear thickened and hyalinized, and their elastic fibrils are distorted. Masson's trichrome stain; ocul., 5 ×; obj., 16 ×.

Fig. 23.—This diagram presents the relation of digital arteriovenous anastomoses found in thrombo-angiitis obliterans and shown by serial sections. The section numbers of the series corresponding to these nine figures are 30, 28, 27, 25, 21, 19, 15, 13 and 9. Section 30 shows a small valvular vein (*V*1) of the stratum reticulare. Section 25 shows below the vein *V*1 a venous space (*V*2) to the left and an arterial slit (*A*1) to the right. In section 15 the vein *V*2 approaches the vein *V*1. In section 13 the veins *V*1 and *V*2 unite and form another vein (*V*3). At the lower left pole of the vein *V*2 is seen an artery (*A*2), which begins in section 21 and enters the vein *V*2 in section 15. The artery *A*1, which is first shown in section 25, approaches the vein *V*1, bends to the right and in section 13 forms a short, wide lateral communication with the vein *V*3. In section 9 and the following sections the artery *A*1 continues as an ordinary artery terminated with a capillary network.

Fig. 24.—The drawing demonstrates two types of anomalous arteriovenous anastomoses found in thrombo-angiitis obliterans. One, to the right and below, presents the lateral type of anastomosis, in which the artery continues and breaks finally into ordinary capillaries. In the other (the terminal type), which is seen below on the left, the artery ends by entering the wall of the vein. The relation to the normal digital arteriovenous anastomosis, or digital glomus, is indicated.

collagenous ring furnished with elastic fibrils is found. This subendothelial collagenous ring becomes thickened and hyalinized, and elastic fibrils appear distorted (fig. 21). The primary subendothelial hyalinization extends later along the entire middle portion of the Sucquet-Hoyer canal, and preglomic arterioles and capillaries become thickened and hyalinized. This is followed by an increase in intermuscular collagenous tissue. The sprouts of collagenic fibrils invade the periglomic clear zone, and the fine network of nonmedullated nerves of the periglomic zone disappears, being replaced by coarse collagenous tissue. Both the epineurium and the perineurium of the periglomic nerve trunks show massive lamellated fibrosis. With the advance of periglomic sclerosis and subendothelial hyaline degeneration of the Sucquet-Hoyer canal and the periglomic arterioles, the primary collecting veins encircling the glomus appear rather voluminous and permanently dilated (fig. 3). The state of the collecting veins mirrors the extent of anatomic destruction and functional disability of the Sucquet-Hoyer canal. The functional disability of this canal puts an abnormal strain on the collecting veins and consequently on the corresponding deeper veins. As a result of this, the veins undergo hypertrophy and assume gradually an arterial character.

In diabetic gangrene degenerative changes of the Sucquet-Hoyer canal are more prominent than those observed in arteriosclerotic gangrene. Obliteration of the Sucquet-Hoyer canal is more common. In a great number of cases the number of these canals is decreased markedly, and sometimes not a single normal glomus can be found. In noncomplicated cases the degenerative changes of the Sucquet-Hoyer canal are not accompanied by lipoidosis, cellular infiltration or thrombosis. Valvular changes of the veins do not differ from those observed in arteriosclerosis. Continuous disturbance in venous drainage results in sclerosis of the skin, atrophy of the cutaneous appendages and hyperkeratosis of the epidermal lining. Chronic stasis in superficial veins leads to the formation of capillary varices (bullae) in papillary bodies and later creates conditions favorable for bacterial invasion.

Thrombo-Angiitis Obliterans.—Five patients with thrombo-angiitis obliterans were examined; all were under 40 years of age. One case was especially instructive, for it enabled me to study all the digits and the leg, these being obtained from two consecutive operations.[11] At the time of the first operation the fourth and fifth toes of the left foot were removed because of ulceration and impending gangrene. Five weeks later, amputation of the leg was performed on account of gangrene of the third toe. In all my cases both the digits affected by gangrene and those now affected were examined. Examination of all the regions was made in accordance with the method already described.

Pathologic changes are distributed unevenly in thrombo-angiitis obliterans, and vary greatly. One pathologic manifestation, which appears to be characteristic of this disease and which is commonly observed in both grossly affected and nonaffected digits, is generalized massive fibrosis. Transformation of fibrillar interstitial connective tissue into swollen collagenous tissue justly permits the use of the term interstitial sclerosis. This sclerosis involves all the zones of the skin. It affects all the appendages of the skin to such an extent that fibrosis and atrophy in very old persons with senile arteriosclerosis may be considered as insignificant.

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11. Dr. Walter A. Calihan of the Highland Hospital of Rochester furnished this case, which was supplemented with a complete history, including a report of all the modern diagnostic methods.

The state of the glomic system varies in different regions of the same digit. In the region where thrombosis and secondary inflammation are absent and where other changes of the skin are not prominent the following histologic picture is seen: The Sucquet-Hoyer canals are free from primary degenerative changes; the intimal and mucsular layers are not altered. When subjected to pressure by surrounding sclerosed tissue, the glomic units appear compressed and diminished in size. The periglomic neuroreticular zone is reduced greatly; dense fibrous tissue encroaches on the capillaries of the preglomic arterioles and the primary collecting veins, and the epineurium and perineurium of the periglomic nerve trunks show extensive lamellated fibrosis. With the exception of massive periglomic sclerosis and sclerosis of the nerve trunks, no other changes are observed which would contribute to functional disability of the Sucquet-Hoyer canals.

In the regions where thrombosis is prominent the glomic system is affected by thrombosis, both directly and indirectly. The thrombi observed in the peripheral digital system are small and multiple. The average length of the thrombi found in the Sucquet-Hoyer canals varies from 25 to 70 microns. As to the location of thrombi, the following peculiarities are observed:

1. The thrombus may be lodged in the afferent artery, obstructing both the Sucquet-Hoyer canals and the preglomic arterioles.

2. The thrombus may be lodged in the Sucquet-Hoyer canal itself, while preglomic arterioles are free from thrombi.

3. The thrombus may be lodged in the afferent artery, obstructing the intramural preglomic arteriole, but not extending into the Sucquet-Hoyer canal (fig. 25).

4. Of several neighboring Sucquet-Hoyer canals formed by the same afferent artery, one may be blocked by a thrombus and the others may remain free from thrombi.

5. The thrombus may be lodged in a perineural or intraneural capillary of one of the periglomic nerve trunks.

The described localization of glomic thrombi and the chance that some of them may be septic contribute to a variety of glomic changes, the functional importance of which is obvious.

The thrombi in the larger deeper arteries are of considerable size, but they are also multiple and are lodged at various levels of the same artery. This facilitates efforts to establish collateral circulation through the vasa vasorum. If proper histologic technic is employed, the vasa vasorum of the digital arteries are seen to penetrate to the intima.

In certain areas the entire arteriovenous system appears altered in a peculiar fashion. The arteries are tortuous and thinned; their intermuscular collagenous tissue is prominent, and, if cut longitudinally, the arteries show regional fusiform dilatation. The veins of both smaller and larger caliber in such regions are widely dilated; their muscular layer is in a hypertrophic state, and elastic tissue is more abundant and is distributed irregularly. Since no local inflammatory or organic obstructive lesions in the glomic system, which could explain the observed vascular changes, were observed in my study, careful examination of sections of a long series was made. On reconstruction of the arteriovenous plexus, it was seen that certain arterial branches of the stratum reticulare and stratum subcutaneum have direct communication with the veins. These communications are entirely different from the Sucquet-Hoyer canals. Two types of arteriovenous communication were seen. In the first type an arterial branch ends by entering the vein through its wall. In the second type an artery which runs parallel to the vein approaches the

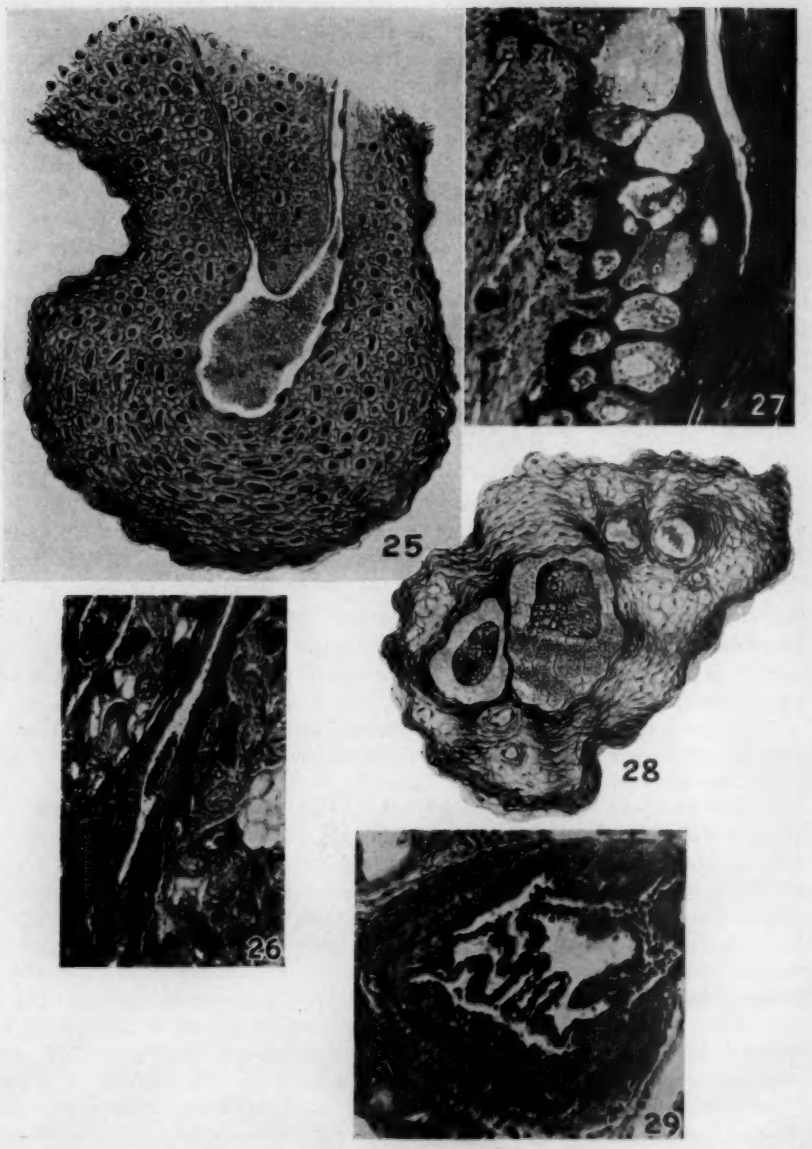

Plate 5

EXPLANATION OF PLATE 5

These figures illustrate various conditions found in thrombo-angiitis obliterans.

Fig. 25.—The thrombus obstructs the afferent artery and in the center extends to the preglomic arteriole (upper right), while the Sucquet-Hoyer canal (upper left) is closed and free from thrombosis. Masson's trichrome stain; camera lucida drawing; ocul., 10 ×; obj., 4 ×.

Fig. 26.—Photomicrograph showing an artery of the stratum subcutaneum, with fusiform dilatation and thrombus due to stagnation. Neither inflammatory nor degenerative changes are seen in the artery at the place of fusiform dilatation. Masson's trichrome stain; ocul., 5 ×; obj., 16 ×.

Fig. 27.—Photomicrograph showing: massive sclerosis of the stratum reticulare; all stages of dilatation of the capillaries, with formation in the papillary bodies of capillary varices lined with prickle cells (hemorrhagic bullae), and extensive hyperkeratosis of the epidermal lining. The entire picture resembles closely angiokeratoma of Mibelli. Masson's trichrome stain; filter H was used to accentuate the capillary varices; ocul., 5 ×; obj., 16 ×.

Fig. 28.—Results of perineural and intraneural capillary varices, indicated on the left by distention of the perineural space and an accumulation in it of acellular fluid (hydroneurocele) and in the center by distention of the perineural space, with hemorrhage into it (hematoneurocele). Masson's trichrome stain; camera lucida drawing; ocul., 10 ×; obj., 9 ×.

Fig. 29.—Photomicrograph showing the valvular vein of the outer zone of the stratum subcutaneum. On the right side, in the lumen, behind the ostial valve is seen an accumulation of inflammatory cells brought by a contributory vein which drains a septic region. Here, behind the valve in the valvular sinus, phlebitis and the formation of a venous thrombus are beginning. Masson's trichrome stain; ocul., 10 ×; obj., 16 ×.

vein closely and forms a short lateral communication leading into it. The artery continues as an ordinary artery and ends with the formation of a capillary network. In the first, or terminal, type of arteriovenous communication the arterial communicating branch is from 0.5 to 1.5 mm. long and from 100 to 250 microns in diameter. In the second, or lateral, type of arteriovenous communication the lateral passage between the artery and the vein is from 200 to 350 microns long and from 100 to 160 microns in diameter.

Figure 23 presents the relation of arteriovenous communications, as shown by serial sections. Section 30 begins with a small valvular vein (*V*1) situated in the inner zone of the stratum reticulare, which continues in sections 28 and 27. In section 25 there appears in the lower extravenous region a small venous space (*V*2) on the left and a small arterial slit (*A*1) on the right. The lower left venous space (*V*2) becomes larger and in section 15 approaches closely the wall of the vein *V*1. At the lower left pole of the vein *V*2 is an artery (*A*2), which begins in section 21 and which is seen entering the vein *V*2 in section 15. In section 13 the septum between the two venous spaces disappears, and veins *V*1 and *V*2 unite and form a large vein (*V*3). The artery *A*1, which is first shown in section 25, on approaching the vein *V*1, bends to the right and in section 13 forms a wide, short lateral communication with an open channel leading into the large vein (*V*3). The artery *A*1 then continues as an ordinary artery and terminates with a capillary network.

The orientation of vessels *A*1 and *A*2, the direction of their branches, the arrangement of the elastic fibrils and the structure of the muscular layer are all characteristic of the arterial type of these vessels. The appearance in serial sections, the type of distribution of the elastic fibrils, the structure of the muscular coat and of the adventitia and the presence of the valves leave no doubt that the vascular spaces *V*1, *V*2 and *V*3 are true veins.

Figure 5 is taken from section 13 of the schematically presented series just discussed (fig. 23). The upper right corner of the large vascular space shows the vein *V*1. The upper left corner of this space shows the vein *V*2, with a distinctly visible valve at its top. The lower part of the vascular space corresponds to the vein *V*3. At the bottom of the venous space *V*3 are seen the artery *A*1 to the right and artery *A*2 to the left. A schematic presentation of the two types of peripheral digital arteriovenous communications is shown in figure 24. This figure indicates the topographic relation of the described anomalous arteriovenous anastomosis to the normal arteriovenous anastomosis, or the normal glomus.

Of particular significance is the fusiform dilatation of the artery proximal to the anastomosis (fig. 5). Though this dilatation is most conspicuous in the region nearest the place where the artery enters the vein, other parts of the anastomotic artery may show fusiform dilatation of similar character. The vein *V*3, which is proximal to the place of arteriovenous union, is considerably dilated, and its wall shows an increase in elastic tissue. The artery at the place of fusiform dilatation shows considerable increase in intermuscular collagenous tissue. The elastic fibrils appear thinned and stretched, but no actual increase in elastic tissue is observed in the dilated portion of the artery.

On further examination, the fusiform dilatations were seen not only in the arterial branches directly communicating with the vein, but in the deeper, larger arteries as well. Since no primary inflammatory or degenerative changes were seen at the places of fusiform dilatation of the arteries, it is evident that the process of dilatation must be slow and must be due to some continuous mechanical interference with normal circulation. The only causative agent that I consider as

fully adequate to explain this interference is an anatomic abnormality manifested by the presence of arteriovenous anastomoses. These anomalous anastomoses are entirely different from the arteriovenous anastomoses which were described by Sucquet and Hoyer and which are normally present in the peripheral digital system.

It must be mentioned once again that the changes of the Sucquet-Hoyer canal in the patients with thrombo-angiitis obliterans whom I examined were not primary and were not sufficient to explain the pathologic phenomena observed. Thrombosis of the larger peripheral arteries was of secondary importance. Thrombi may be absent entirely, and yet arterialization of the veins, regional fusiform dilatation of the arteries and other signs of venous stasis may be conspicuous. Sometimes a thrombus is lodged at the place of fusiform dilatation, but neither inflammatory nor degenerative changes of the arterial wall are seen at the point of dilatation (fig. 26). This indicates that such a thrombus is of the type due to stagnation and the lodging of the thrombus in the dilated portion of the artery is due primarily to a mechanical factor causing general slowing of arterial circulation.

Arterialization of the veins is evidently the result of adaptation of the veins to abnormal strain created by an uncontrollable flow of arterial blood through the arteriovenous anastomoses. The existence of anomalous anastomoses explains the mechanism of venous stasis and its sequence, manifested by interstitial sclerosis (sclerodactylia) and atrophy of the cutaneous appendages. The capillaries of the papillary bodies affected by generalized vascular stasis are distended, and large capillary varices are formed in the papillary bodies. If the papillary body contains more than one capillary, the vascular cavity appears divided by septums. As the result of pressure atrophy the connective tissue of papillary bodies disappears, and a vascular cavity lined with prickle cells of the epidermal layer is formed. The horny layer is extremely thickened. At this stage the histologic picture is similar to that of angiokeratoma of Mibelli (fig. 27). Stagnating material of such peripheral capillary varices (bullae) offers a good medium for bacterial growth.

As a result of chronic venous stasis, distention of the perineural and intraneural capillaries of both the smaller and the larger nerve trunks takes place. The formation of perineural and intraneural capillary varices is followed by local interference with the flow of fluid along the epineural and perineural spaces. The nerve trunks in such regions appear surrounded by a wide space filled with clear acellular fluid. If hemorrhage takes place, the wide perineural space appears filled with blood (fig. 28). Considering the classic work of Key and Retzius [12] and the recent work of Funaoka [13] on the flow of fluid in epineural and perineural spaces in the peripheral nerves, it is permissible to use for the conditions described the terms peripheral hydroneurocele and hematoneurocele.

The valves of the veins play a double mechanical rôle. They direct the flow of blood brought by individual smaller veins coming from different regions, and they protect the distal venous column from abuse. In thrombo-angiitis obliterans the valves of dilated and hypertrophied veins appear thickened and hyalinized, with the elastic fibrils distorted. Since head pressure from the anomalous arteriovenous anastomosis continues, the burden of the valves becomes increasingly heavy, and this leads gradually to valvular insufficiency. If one of the contributory veins drains a region affected with inflammation, the larger collecting vein shows an accumulation of inflammatory cells behind the corresponding valve only (fig. 29).

12. Key, A., and Retzius, G.: Studien in der Anatomie des Nervensystems, Arch. f. Micr. Anat. **9**:308, 1873.

13. Funaoka, S., quoted by Hassin, G.: Arch. Neurol. & Psychiat. **27**:58, 1932.

Phlebitis and incipient formation of a venous thrombus begin in the valvular sinus, i. e., behind the valve which directs the blood coming in from the septic region.

Supernumerary Digits (Pedunculated Postminimi) in Man.—Slides from 17 cases of Cummins were examined, the patients ranging from those stillborn at term to those aged 4 days. Only 1 infant was 2 weeks of age. All the details of the histologic observations can be found in the paper by Cummins.[9] My studies were limited mainly to the state of the glomic system, and in the slides examined I was unable to observe anatomic structures which would correspond to the arteriovenous anastomoses of the Sucquet-Hoyer type.

COMMENT

The digital glomus presents a specifically constructed and specifically located system. This system differs from the ordinary circulation, in which arteries and veins are reunited by capillaries. The Sucquet-Hoyer canal is a main part of the glomus. Other constituents of the glomus are: an afferent artery; a periglomic, clear neuroreticular zone; preglomic arterioles; periglomic nerve trunks; an outer, lamellated collagenous zone, and the primary collecting veins. Such an anatomic concept is helpful for proper understanding of the normal function of the Sucquet-Hoyer canal. In pathologic conditions each of the aforementioned constituents of the glomus can be an initiating point in the change of the entire glomic unit.

The glomus serves two functions—local and general. If the digits are exposed to cold, it is through the agency of the glomic system that local temperature is maintained and even raised. This is accomplished by diverting blood from the capillaries and rushing it through anastomoses into collecting veins with a highly developed surface area. If, owing to mechanical pressure or other influence, the peripheral arterial pressure becomes abnormally high, the anastomotic by-passages divert the arterial blood and thus relieve the peripheral arterial system of an extra burden. If the peripheral veins and venules are unable to cope with the influx of blood, the anastomoses, by sending a part of the blood directly into the deep veins, help in correcting local disturbances in the venous circulation. Recent investigations by the physiologic school of Lewis [14] prove convincingly that the glomic system also forms an important factor in the mechanism for regulating the general temperature of the body. When fully opened, it aids the dispersal of heat by allowing an enormous flow of blood to pass through the digits. When closed, it reduces the dispersal of heat to the maximum physiologic limit.

The absence of the glomic system in a fetus aged from 5 months to term indicates that this system evidently is not needed in fetal life.

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14. Lewis, T., and Pickering, G.: Heart **16**:33, 1931. Grant.[7a] Grant and Bland.[7b]

Development of the glomic system takes place within the first months of postnatal life. It is known that regulation of heat is one of the least developed functions of premature infants. The body temperature of such infants shows marked fluctuations, with a tendency to hypothermia. This is usually attributed to the following conditions: (1) lack of development of the nervous system and especially of the respiratory center, (2) loss of heat through radiation, (3) weak cardiac action, (4) insufficient combustion of oxygen and (5) improper metabolism. Both anatomic and physiologic knowledge of the glomic system reasonably suggest that the poor control of body temperature in premature infants may be due primarily to absence of the peripheral glomic system. Retarded and improper development of the glomic system in normal infants born at term contributes greatly to the deficiency in controlling the local and general temperature of the body.

In a normal adult each integral part of the glomus is anatomically well differentiated. Each constituent works as a part of one functional unit. Close anatomic and physiologic interrelation of all constituents explains the liability of the glomus to various changes. Regeneration and development of a new Sucquet-Hoyer canal is possible. Generally speaking, formation of new capillaries and subsequent transformation of capillaries into veins and arteries or into an adult vascular pattern is of common occurrence (Clark,[15] Sandison[16]). The process of development of a new and functionally efficient Sucquet-Hoyer canal is much more complicated than an ordinary capillary transformation under experimental conditions. Development of a new canal takes place only in a zone normally occupied by a glomic unit. Preglomic arterioles form a foundation for development of a new canal. These arterioles are part of the afferent glomic artery. They are short and open into specifically orientated veins characterized by a highly developed surface area. They are in close relation to the clear periglomic neuroreticular zone and the periglomic nerve trunks. Such anatomic coordination is most favorable for the development of a new and functionally efficient glomus from preglomic arterioles.

The presented concept on the anatomy of the normal glomus permits one to establish certain differential points in the pathologic anatomy of diseases affecting the digits. In inflammation the digital glomus presents a *locus minoris resistentiae*. Functionally sensitive to thermic, mechanical, chemical and neural influences, the glomus initiates changes leading to venous stasis over the area affected. Stasis in primary collecting veins interferes with the drainage of preglomic arterioles and is followed by inflammatory cellular infiltration into the clear periglomic zone and muscular wall of the Sucquet-Hoyer canal. Loosely arranged,

15. Clark, E.; Hitschler, W. J., and others: Anat. Rec. **50**:129, 1931.
16. Sandison, J.: Am. J. Anat. **41**:475, 1928.

lacking in elastic tissue support and poor in intermuscular collagenous tissue, the muscular cells of the Sucquet-Hoyer canal acquire an embryonal ameboid character and gradually move into periglomic connective tissue. As the result of such regressive remodeling, the Sucquet-Hoyer canal is transformed into a large, distended capillary surrounded with inflammatory elements and containing only a few pyknotic cells. In case of recovery, progressive remodeling, i. e., transformation of the affected Sucquet-Hoyer canal, into the proper glomic pattern takes place. Senile arteriosclerosis affects chiefly the digital arteries of larger caliber. Hyalinization of the afferent glomic arteries is part of a general pathologic process involving all the digital arteries. With the advance of hyaline changes of the afferent glomic artery, the endotheliomuscular elevations, located at the point of origin of the Sucquet-Hoyer canal and the preglomic arterioles, become flattened. This produces functional incapacitation of the proximal part of the Sucquet-Hoyer canal. Extension of hyaline changes to the preglomic arterioles leads to disturbances in nutrition of the entire glomus, including the periglomic nerve trunks. The wall of the Sucquet-Hoyer canal proper retains its structural characteristics for a long time, indicating that this canal is not primarily involved in senile arteriosclerosis. Beginning functional disturbances are due to hyaline changes of the afferent artery, and the anatomic deterioration of the glomus in cases not complicated by inflammation is the result of gradual atrophic changes of all the constituents of the glomus.

Comparative studies on the state of the glomic system in arteriosclerotic and diabetic gangrene do not permit consideration of these two processes as absolutely identical. Current opinion is that the pathologic changes of the vessels in arteriosclerosis and diabetes are the same. Gangrene, according to this opinion, is not due to diabetes per se but to a mortifying process dependent on extensive arteriosclerosis. This opinion is based on comparative observations in large arteries and large veins. The majority of the cases of diabetic gangrene are complicated by either secondary inflammation or arteriosclerosis. But if all the digits and all the regions of each affected and nonaffected digit are examined systematically, it becomes difficult to attribute the entire variety of changes observed to sclerosis of the large arteries as a sole cause. If, in cases of diabetes, the digital regions free from gangrene and sclerotic changes in the afferent glomic artery are examined, it is seen that the Sucquet-Hoyer canal and the preglomic arterioles are the first to show signs of primary degenerative change. The intima of the Sucquet-Hoyer canal appears thickened and hyalinized. This degenerative process begins in the proximal part of the canal and extends along the intima of the entire anastomotic passage. In arteriosclerosis the digits free from gangrene and secondary inflammation may not show any appreciable changes in the wall of the

Sucquet-Hoyer canal. Formation of subepithelial hemorrhagic bullae is seen in arteriosclerosis and diabetic gangrene. In both diseases these bullae are due to capillary varices in papillary bodies, caused by functional collapse of the Sucquet-Hoyer canal and consequent interference with the venous drainage over the area affected. Depending on the extent and duration of changes in the Sucquet-Hoyer canal, the corresponding veins undergo dilatation and hypertrophy and become gradually arterialized.

In thrombo-angiitis obliterans no primary degenerative or inflammatory changes of the Sucquet-Hoyer canal are observed. In areas affected by thrombosis the individual glomic units may be the seat of thrombi. The topographic varieties of the glomic thrombi which have been described contribute to the pathologic peculiarities of the glomus affected. It is evident that local changes of the glomus are due either to glomic thrombi or to atrophy caused by generalized interstitial sclerosis of surrounding tissues. Neither generalized interstitial sclerosis nor the vascular changes seen can be explained by observations in the glomic system alone. Nothing is seen that would permit consideration of inflammation of the vessels or of thrombosis as a causative agent. Comparative studies of my entire material show that digital changes in thrombo-angiitis obliterans are specific and must be due to some other cause. On examination of serial sections of all the regions of grossly affected and nonaffected digits, it was seen that the mechanism underlying the entire pathologic picture must be attributed to a vascular anomaly manifested by the presence of arteriovenous anastomoses entirely different from those described by Sucquet and Hoyer. Peripheral venous stasis, dilatation and arterialization of the veins, thinning and hyalinization of the arteries, fusiform dilatation of the arteries and general atrophic changes appear as a sequence of conditions created by continuous deviation of arterial blood through anastomoses into the veins.

This observation involves the general question of arteriovenous anastomoses. Anatomically, arteriovenous anastomoses are divided into two groups. To the first group belong the arteriovenous anastomoses of Sucquet-Hoyer. These peripheral anastomoses, which are present in normal conditions, are characterized by their coiled, twisted appearance, by their peculiar structure which differs from the structure of arteries, veins and capillaries and by their diameter which never exceeds 0.1 mm. In man these anastomoses are under control of vasomotor nerves, and their function is to divert rapidly the flow of blood from the artery directly into the veins. For this reason Sucquet chose for these anastomoses the name *canaux dérivatifs*. In case pressure in the arteries and veins becomes high, these anastomoses reestablish normal pressure by opening their communications between the two systems.

In addition, by the same mechanism of opening and closing, they regulate both the local and the general temperature.

The arteriovenous anastomoses of the second group are the direct anastomoses between arteries and veins of larger caliber. In lower animals arteriovenous anastomoses are common. In man arteriovenous anastomoses are always present before birth. Chemical proof of the existence of arteriovenous anastomoses is demonstrated by the high unsaturation of fetal blood in respect to oxygen, which indicates that at term the fetus exists normally in the state of cyanosis (Eastman [17]). In the adult human being arteriovenous anastomoses are rare, and they are considered as a vascular anomaly. All varieties, described both as to type and as to topographic distribution, have been reported in the literature (Tschausoff,[18] Gérard,[19] de Takáts,[20] de Takáts and Mackenzie,[21] Szepsenwol,[22] Miller and Godfrey [23] and others).

Experiments on reproduction of arteriovenous anastomotic anomalies began with the classic work of Carrel and Guthrie.[24] Their experiments demonstrated the remarkable adaptability of arteries and veins to mechanical conditions created by reversing the circulation. Reid [25] has studied systematically the effect of arteriovenous fistulas on the heart and blood vessels. His work includes experimental and clinical investigations, and his observations serve to explain certain observations in my material. He noted that the wall of the vein involved in an arteriovenous fistula becomes dilated and hypertrophied (arterializes) and that an arteriovenous fistula of long duration usually causes dilatation of the artery proximal to the fistula. Callander's [26] publication presents a thorough review of 447 cases of arteriovenous fistulas, with a detailed discussion of their physiology and pathologic anatomy. Of all the theories cited by Callander which are offered as an explanation of arterial dilatation, that of Delbet sounds most reasonable. According to Delbet, the dilatation and thinning of the artery are to be explained on the basis of atrophy of disuse, as the artery in the presence of arteriovenous anastomosis no longer needs to contract against the customary arterial pressure. Among other phenomena associated with arteriovenous fistulas, Callander mentioned a variety of nutritive and

17. Eastman, N.: Bull. Johns Hopkins Hosp. **47**:221, 1930.
18. Tschausoff, M.: Medicinischer Bote no. 15 (in Russian), quoted by Hoyer: Jahrb. f. Anat. u. Physiol. **3**:176, 1874.
19. Gérard, G.: Arch. de physiol. norm. et path. **7**:597, 1895.
20. De Takáts, G.: Surg., Gynec. & Obst. **55**:227, 1932.
21. De Takáts, G., and Mackenzie, W.: Surg., Gynec. & Obst. **58**:655, 1934.
22. Szepsenwol, J.: Arch. d'anat., d'histol. et d'embryol. **15**:45, 1932.
23. Miller, N., and Godfrey, J.: Anat. Rec. **13**:177, 1917.
24. Carrel, A., and Guthrie, C.: Compt. rend. Soc. de biol. **58**:730, 1906.
25. Reid, M.: Bull. Johns Hopkins Hosp. **31**:43, 1920.
26. Callander, C.: Ann. Surg. **71**:428, 1920.

other changes furnished by obstruction of venous return, including edematous infiltration and hypertrophy of the extremities, hypertrophy of subcutaneous tissue followed by subsequent atrophy of the skin, hypertrophy of the hair and nails, a sense of chilliness and cold in the part at or below the region of anastomosis and spontaneous gangrene of the foot and leg. In the light of my observations, all these changes are of special significance.

In pediatric literature the question of trophic changes and spontaneous gangrene are discussed more clinically than pathologically. The pathologic reports are vague and incomplete. Peckham,[27] in a statistical study of 1,461 stillborn fetuses, found that in 28 per cent the cause of death was not demonstrated, and in 19 per cent death was attributed simply to asphyxia. It appears that if the search for vascular anomalies were made more carefully, the diagnosis of asphyxia could be reduced considerably. Fitzwilliams and Vincent [28] reported gangrene of the leg in an 11 day old infant in whom the only change was thickening of the intima of the vascular wall. Thickening of the intima and increase in elastic tissue are characteristic of the first stage of thrombo-angiitis obliterans. According to Krompecher,[29] the increase in elastic and fibrous tissue (*Elastofibrose*) leads to narrowing of the small vessels and is specific for the first stage of thrombo-angiitis obliterans. In view of this, Krompecher called the entire process *Teleangiostenose*. Increase in elastic tissue he attributed to the abnormal activity of vascular elastoblasts. He observed that *Teleangiostenose* affects both the arteries and the veins, and he considered hereditary degeneration of the mesenchymal tissue (*mesenchymale Heredodegeneration*) as a possible etiologic factor. Carrel and Guthrie [24] produced thickening of the intima, increase in elastic tissue and hypertrophy of the muscle cells by diverting arterial blood into the veins. By reversing the circulation, Carrel was able to transform veins into pulsating arteries and arteries into flaccid veins. In the light of these experiments, it is difficult to attribute Krompecher's *Teleangiostenose* to inborn primary overactivity of elastoblasts. Thickening of the intima in thrombo-angiitis obliterans is the result of neither arteriosclerosis occurring with advancing age nor thrombosis with canalization (Brown, Allen and Mahorner [30]).

My studies on the state of the digital vascular system show that certain changes in arteries and veins disclose nothing but functional

27. Peckham, quoted by Eastman.[17]

28. Fitzwilliams and Vincent, quoted by Grulee, C. G.; Bonar, B. E., and Haynes, R.: Clin. pediat. **3**:118, 1926.

29. Krompecher, S.: Beitr. z. path. Anat. u. z. allg. Path. **85**:647, 1930.

30. Brown, C.; Allen, E., and Mahorner, H.: Thrombo-Angiitis Obliterans, Philadelphia, W. B. Saunders Company, 1928.

adaptation necessitated by altered mechanical conditions. If Sucquet-Hoyer's arteriovenous anastomosis becomes inefficient, it plays the rôle of a functionally uncontrollable arteriovenous fistula, and, depending on the degree of disability and the duration of the uncontrolled activity of the Sucquet-Hoyer canal, the arteriovenous system of the region involved is changed accordingly. The dependent tissues show all signs of trophic disturbance. This happens in inflammation, arteriosclerosis, diabetic gangrene and thrombo-angiitis obliterans. In thrombo-angiitis obliterans I observed, in addition to localized vascular changes caused by collapse of the Sucquet-Hoyer canal, generalized arteriovenous pathologic changes which were unrelated to the Sucquet-Hoyer system of peripheral anastomoses. Thickening of the intima, increase in elastic tissue, fusiform dilatation of the arteries and dilatation and arterialization of the veins are not limited to a zone occupied by Sucquet-Hoyer's anastomoses. The trophic changes are more diffuse and pronounced than those caused by collapse of Sucquet-Hoyer's anastomoses. I attribute these changes to the peripheral arteriovenous anastomoses. These anastomoses are entirely different from those described by Sucquet and Hoyer, and I consider them as a vascular anomaly.

In looking over descriptions of symptomatology in thrombo-angiitis obliterans, it is significant that local chronic cyanosis of the toes may precede gangrene of the foot by months and even years and may be the only objective sign of the disease. Postural color changes in the earliest stages of thrombo-angiitis obliterans occur only in the tips of the toes. Pain while the patient is at rest occurs almost exclusively in the digits and appears before obvious trophic changes can be observed. Coldness of the extremities is described as an annoying and persisting complaint. It is noteworthy also that in 71 of 100 cases of thrombo-angiitis obliterans both lower extremities were involved (Buerger [8]). Since no definite toxic etiologic agent of thrombo-angiitis has been found, infectious and constitutional factors are considered in the literature. Krompecher's [29] concept of *mesenchymale Heredodegeneration* is directed toward a constitutional anomaly. Gruber [31] considered the inborn constitutional peculiarity of the reaction of the blood vessels as a possible etiologic factor. All the peculiarities of the changes in arteries, veins, glomus and capillaries and all the trophic changes of the skin and cutaneous appendages, including the peripheral nerve, in the cases of thrombo-angiitis obliterans studied by me I attribute directly to the presence of the anomalous arteriovenous anastomoses described.

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31. Gruber, G.: Ztschr. f. Kreislaufforsch. **23**:537, 1931.

In the search for chemical proof of the existence of arteriovenous anastomoses, a comparison of the gaseous content of the blood from the venous arch of the dorsum of the foot, the lower portion of the internal saphenous vein of the foot and the median basilic vein of the arm was made on a patient with thrombo-angiitis obliterans. The blood was taken at normal room temperature, at the same time, with identical technic and while the patient's breathing was shallow, regular and of the usual frequency. The carbon dioxide content, oxygen content, oxygen combining power and oxygen saturation were determined. The readings for the blood from the veins of the affected foot just indicated were: oxygen content, 16.95 per cent, and oxygen saturation, 82.49 per cent. The comparative readings for the blood from the median vein of the arm were: oxygen content, 13.17 per cent, and oxygen saturation, 63.9 per cent. Although the other factors (Goldschmidt and Light [32]) which may influence the gaseous content of the peripheral blood were kept in mind, the comparative readings obtained are of significance. Both the color and the gaseous content of the blood from the veins of the affected foot indicate that the blood examined was mixed arteriovenous blood. The observation of an anomalous peripheral arteriovenous anastomosis offers a reasonable explanation for the changes observed in the venous blood examined.

The difference between normally found peripheral anastomoses of the Sucquet-Hoyer type and the accidental arteriovenous anastomoses of the type of vascular anomaly are summarized in the table.

My studies on the state of the digital glomic system and my observations of the vascular anomaly, manifested by the existence of arteriovenous anastomoses, suggest the need for more careful examination of the vascular system in regard to the anomalies in my material. The search for peripheral arteriovenous anastomoses requires proper fixation of fresh material, trichrome staining controlled by staining for elastin, examination of all the affected and nonaffected digits and careful reconstruction from uninterrupted, long series of sections. The injection method may be tried, but perfectly fresh material should be used, and the observations should be controlled by the method of reconstruction from serial sections. In my normal and pathologic material, covering 840 individual blocks, I observed abnormal digital arteriovenous anastomoses only in cases of thrombo-angiitis obliterans.

The comparative results of my studies on the digital glomus demonstrate that neurovascular and trophic changes observed in the digits in many instances may be due primarily to local changes in the glomus and not to inflammatory, degenerative or obstructive changes in the large arteries and veins of the extremities. It must be kept in mind

32. Goldschmidt, S., and Light, A.: Am. J. Physiol. **73**:127, 146 and 173, 1925.

Comparative Observations in Sucquet-Hoyer's Anastomoses and Anastomoses of the Type of Vascular Anomaly

	Normal Peripheral Sucquet-Hoyer's Anastomoses of the Extremities	Digital Arteriovenous Anastomoses of the Type of Vascular Anomaly
Distribution	Ventral and lateral parts of the digits, nail bed, nail matrix, thenar and hypothenar eminences of the hand and sole near the heel	The inner zone of the stratum reticulare and the stratum subcutaneum
Appearance	Coiled, twisted, S-like and seldom straight; afferent artery forms from one to four individual anastomoses	Mostly straight; single; of directly terminal or lateral type
Size	The lumen does not exceed 0.1 mm.; average length is from 0.5 to 0.8 mm.	The lumen is larger than 0.1 mm.; the size varies with the caliber of the communicating vessels and the type of anastomosis
Structure	The afferent artery has endotheliomuscular elevations, which direct the flow of the blood into anastomoses and preglomic arterioles; with the exception of its proximal part, the anastomosis has no elastic lamina; the muscular cells of the wall are specific in structure and arrangement; the perianastomotic region is surrounded with a wide clear neuroreticular zone (expansion zone); the primary collecting veins are shaped like a long broad ruffle; they encircle the glomus and present a voluminous receptaculum with a highly developed surface	The lumen of the proximal part of the anastomosis does not show endotheliomuscular elevations; the structure of the anastomosis is that of the ordinary artery; the structural changes are secondary and are caused by altered mechanical conditions; the structure and shape of the collecting vein are those of an ordinary vein; hypertrophy and dilatation of corresponding collecting veins are secondary
Control	The contraction and dilatation of the anastomosis are under perfect control of the local and general vasomotor mechanism	Local and general vasomotor control is only relative and never perfect
Function	Adjusts peripheral arteriovenous system to changes caused by internal and external influences; controls local arterial and venous pressure; regulates local and general temperature	Purposeless and detrimental
Results of Functional Disability	When in a state of functional disability, the opened anastomosis pours the arterial blood continuously into primary collecting veins; the latter become hypertrophied and dilated; subpapillary and corresponding deep veins of the region affected undergo hypertrophy and dilatation, with generalized peripheral venous stasis; all the mesodermal and ectodermal constituents of the region involved show secondary trophic changes; control of local temperature and, to some extent, of general temperature, is deranged	Lacking in normal vasomotor control and having a larger diameter than a normal anastomosis, the anomalous anastomosis precipitates more profound changes; the gaseous content of the blood becomes abnormal; the arteries show regional fusiform dilatation, which is more conspicuous in the portion of the anastomosis near the vein; the collecting veins undergo arterialization and dilatation; venous stasis is pronounced; peripheral venous stasis leads to the formation of intrapapillary varices (hemorrhagic bullae); the extent of the secondary trophic changes depends on the position and diameter of the anastomosis and the duration of its existence; trophic changes lead gradually to progressive scleroderma, perineural fibrosis and atrophy of the cutaneous appendages and terminate finally with necrobiosis; the temperature in the part at or below the region of the anastomosis is uncontrollable

that changes in the glomic system and the occasional existence of other abnormal arteriovenous anastomoses introduce disturbing elements into the interpretation of capillaroscopic observations of the digits. The local clinical manifestations and diagnostic tests cannot be understood properly without taking into consideration the state of the glomic system and possible anomalies of the peripheral digital vascular system.

SUMMARY

The digital glomus is a normal anatomic unit consisting of: (1) an afferent artery; (2) a Sucquet-Hoyer canal, or arteriovenous anastomosis proper; (3) preglomic arterioles, nourishing all the constituents of the glomus; (4) a clear periglomic zone, or expansion zone, furnished with a neuroreticular mechanism which controls the function of the Sucquet-Hoyer canal; (5) a specially arranged system of collecting veins, and (6) an outer lamellated collagenous zone surrounding the entire glomus.

The function of the glomus is to control arteriovenous circulation in the digits and to regulate both the local and the general temperature of the body.

The digital glomus is absent during intra-uterine life, and is formed shortly after birth. Both trophic and thermic disturbances, which are common in premature infants and which are found after birth in some infants born at term, may be reasonably attributed to absence or improper development of the glomic system.

No glomus is found in supernumerary digits (pedunculated post-minimi) in man.

In advanced senility the glomic units undergo atrophy, and their number decreases with age.

The glomus is sensitive to various influences and presents a very unstable unit. It may show both regressive and progressive changes. In case of complete collapse and deterioration of the Sucquet-Hoyer canal, a new canal can develop from one of the preglomic arterioles described.

Comparative studies of the state of the glomus in arteriosclerotic and diabetic gangrene indicate that the changes observed in the glomus in these two conditions affect the glomus in different ways. In arteriosclerotic gangrene the changes in the glomus are due primarily to hyaline degeneration in the afferent artery of the glomus. In diabetic gangrene the intima of the Sucquet-Hoyer canal and that of preglomic arterioles are the first to show signs of primary degenerative changes, while the intima of the afferent artery of the glomus remains intact.

In the cases of thrombo-angiitis obliterans studied, nothing was observed that would permit consideration of inflammation of the vessels or of thrombosis as a causative agent. The glomic system

appeared to be free from primary specific changes. The changes observed in arteries, veins and capillaries, the trophic changes of the skin and cutaneous appendages, the inflammatory and necrobiotic changes in the digits I attribute directly to a hitherto unknown vascular anomaly of the peripheral digital system. This anomaly is manifested by the presence of abnormal communications, or anastomoses, between peripheral arteries and veins of the digits. Two types of abnormal anastomoses are seen: a lateral and a terminal type. In their size, structure, and topographic distribution, they differ entirely from the normal peripheral digital anastomoses of the Sucquet-Hoyer type.

Consideration of the state of the glomic system and of the anomalous arteriovenous anstomoses described offers a substantial help for an understanding of the vascular and trophic changes observed in the digits.

It is obvious that the action of chemical substances, the capillaroscopic observations, the local clinical manifestations and the results of various diagnostic tests applied to digits cannot be interpreted properly without taking into consideration the anatomic concepts presented.

MYOCARDIAL CHANGES IN HYPERTENSION

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That hypertension, or abnormally high blood pressure, is linked with hypertrophy of the heart has long been understood. Strangely enough, agreement has not been reached as to what other changes, aside from the hypertrophy, occur in the hypertensive heart. There have been varying opinions even in regard to the mode of enlarging. Pathologists and anatomists first believed that the number of muscle fibers increased. Then the view was favored that the muscle fibers increased in size as well as in number. More recently, Karsner, Saphir and Todd [1] have shown that the muscle fibers increase in size but not in number.

MacKenzie [2] stated that there is an absence of correlation between clinical and pathologic findings in cases of nonvalvular hypertrophy of the heart, the type commonly spoken of as hypertensive hypertrophy. Tawara [3] could find no histologic equivalent of acute cardiac failure. Christian [4] stated that nothing abnormal is found in the myocardium, aside from hypertrophy. Cohn,[5] on the other hand, believed that definite changes, such as fibrosis, occur on a noninflammatory basis.

According to Christian,[4] hypertrophy is an unfavorable clinical sign, pointing to a poor prognosis. He stated that once a heart begins to enlarge, changes start which regularly progress to cardiac decompensation. Fitz Hugh [6] agreed with this idea; he found that hearts weighing over 600 Gm. fail more rapidly than smaller hearts.

Clinically, when a heart without valvular lesions "fails," the condition is called "chronic myocarditis." This is a poor term, however, as Cohn [5] and Bierring [7] pointed out, because there is no inflammatory basis for

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1. Karsner, H. T.; Saphir, O., and Todd, T. W.: Am. J. Path. **1**:351, 1925.
2. MacKenzie, J.: Diseases of the Heart, New York, Oxford University Press, 1918.
3. Tawara, S.: Das Reizleitungssystem des Säugetierherzens, Jena, Gustav Fischer, 1906.
4. Christian, H. A.: J. A. M. A. **91**:549, 1928.
5. Cohn, A. E.: Am. J. M. Sc. **177**:619, 1929.
6. Fitz Hugh, G.: New England J. Med. **203**:201, 1930.
7. Bierring, W. L.: J. A. M. A. **101**:663, 1933.

the changes. Riesman [8] and Bierring [7] prefer the term myocardiosis, and Brown [9] offered the terms scarring of the myocardium or myocardial fibrosis as preferable.

Fibrosis of the myocardium is a condition which has been studied since Morgagni [10] first reported a case. Ricord [11] and Virchow [11] called attention to the influence of syphilis in its causation. Ziegler,[12] Turner [11] and Martin [11] pointed out the importance of coronary disease. Brown,[9] in a recent study on the pathogenesis of myocardial fibrosis, divided the causes into three general groups: infectious myocarditis, toxic myocarditis and interference with the blood supply.

By the term myocardial fibrosis in this study is meant the definition which Clawson [13] gave of atrophy of muscle fibers and replacement by scar tissue. Most typically the fibrous tissue is arranged in small islands which often enclose single muscle fibers or fragments of fibers in various stages of atrophy and degeneration.

Because of the lack of agreement as to the myocardial changes in hypertension this study was undertaken. Special attention is given to myocardial fibrosis, because I have frequently observed widespread minute macroscopic and microscopic scars in hypertensive hearts.

STATISTICS

This study was made on 27 hearts chosen from a group of 327 hearts of adults after postmortem examinations performed at the Cook County Hospital. These 27 are 8.2 per cent of the total, which gives an idea of the incidence of hypertension among that group of adults.

The 27 hearts were chosen on the basis of weight. With 3 exceptions (cases 9, 11 and 15), all weighed 500 Gm. or more. In the 3 exceptions the weight was only slightly under 500 Gm. This weight was considered indicative of hypertensive hypertrophy. Hearts with old rheumatic deformities of the valves were not studied in order to keep clear of any old myocardial inflammatory lesions. The hearts were fixed in toto in a 10 per cent solution of formaldehyde for two days. Then blocks were cut from seven places, namely, the anterior and posterior walls of the left ventricle, the large anterior papillary muscle in the left ventricle, the interventricular septum near the apex, the anterior wall of the right ventricle and both auricles. Sections from these locations were stained with van Gieson's stain and studied for myocardial fibrosis, which was classed from a trace to four plus, when present. The degree of endocardial sclerosis was also noted. The medium-sized and smaller arteries and the arterioles were studied in all the sections. Representative sections were stained with Weigert's elastic tissue stain.

8. Riesman, D.: M. Clin. North America **10**:361, 1926.
9. Brown, M. R.: Am. J. M. Sc. **184**:707, 1932.
10. Morgagni, J. B.: De sedibus et causis morborum, Naples, 1762.
11. Quoted by Cowan.[21]
12. Ziegler, E.: Deutsches Arch. f. klin. Med. **25**:586, 1880.
13. Clawson, B. J.: Am. Heart J. **4**:1, 1928.

RESULTS

In the table are listed the essential data in each case. The case number, race, sex, age and blood pressure are given in the first five columns. Next in order are the weight of the heart in grams, the thickness of the left ventricle in millimeters, the thickness of the right ventricle in millimeters, any related myocardial or vascular changes and the cause of death.

In the next column the amount of sclerosis of the large coronary arteries is listed, being classed as marked, moderate or slight. The next seven columns give the amount of changes in the medium-sized arteries. For convenience the sections are numbered from 1 to 7. The next seven columns of the table list the microscopic changes in the smallest arteries and the arterioles, which are listed together because they are considered a functional unit. In grading all the arteries and arterioles, the degree of sclerosis was considered from the point of view of the amount of narrowing of the lumen of the vessel. Four plus sclerosis was taken to indicate complete occlusion, and three plus almost complete occlusion.

In the next seven columns the amount of interstitial fibrosis is given for all the sections. It will be noticed that in very few sections was there a complete lack of fibrosis. None of the hearts showed a total lack of fibrosis. Examples of fibrosis are shown in figures 1 and 2.

SUMMARY OF OBSERVATIONS

The observations which attract most attention are the amount and distribution of the myocardial fibrosis and the relation of the latter to the arterial changes. Clawson [13] and Hunter [14] recently claimed that the fibrosis is proportional to the amount of sclerosis in the coronary arteries. Examination of the table will quickly show that this is not the case here. Only 6 hearts had marked sclerosis of the large coronary arteries; 4 had moderate, and 17 slight, sclerosis. Only 1 heart had marked sclerosis of the medium-sized arteries (those too small to be opened with a pair of scissors and less than the diameter of a low power field of 100 magnifications), and 8 had slight changes in these vessels. In the remaining 18 hearts no changes could be discerned in the medium-sized arteries. On examining the smallest arteries and arterioles, it was observed that 6 hearts had marked arteriolosclerosis in one or more sections (fig. 1), 13 had a slight and insignificant degree of arteriosclerosis and 8 had no changes in these vessels.

Only those cases with marked sclerosis in the arterial tree were considered to show enough anatomic evidence of an interference with

14. Hunter, O. B., quoted by Brown.[9]

TABLE 1.—*Main Clinical Data and Gross Cardiac*

Case	Race	Sex	Age	Blood Pressure	Weight of Heart, Gm.	Thickness of Left Ventricle Mm.	Thickness of Right Ventricle, Mm.	Related Myocardial or Vascular Changes	Cause of Death	Degree of Sclerosis of Large Coronary Arteries
1	W	M	73	220/160	650	20	4	Left ventricle thinned to 3 mm. at apex, mural thrombi in left ventricle, myomalacia in region of left papillary muscle	Cardiac failure	Marked
2	C	M	33	180/130	650	18	6	Left ventricle thinned to 3 mm. at apex, mural thrombi in left ventricle	Cardiac failure	Slight
3	C	M	64	265/158	580	20	3	Left ventricle thinned to 3 mm. at apex, bundle branch block clinically (verified microscopically)	Cardiac failure	Slight
4	C	M	67	184/104	550	20	5	Calcification of aortic ring, dissecting aneurysm of aorta	Spontaneous rupture of aorta	Marked
5	C	M	46	160/125	705	19	7	Moderate atheroma of the aorta, syphilitic aortitis	Cardiac failure	Marked
6	W	F	52	.....	570	25	5	Marked atherosclerosis of aorta, syphilitic aortitis with aneurysm of arch	Cardiac failure	Slight
7	C	F	29	274/168	530	25	5	Chronic glomerulonephritis	Renal insufficiency (uremia)	Slight
8	W	M	53	190/140	630	15	3	Mural thrombi in left ventricle....	Cardiac failure	Slight
9	W	M	88	170/110	475	17	6	Marked sclerosis of mitral ring, sclerosis at aortic ring, aneurysm of left ventricle, thrombi in left iliac vein and right pulmonary artery	Cardiac failure	Slight
10	W	M	54	260/152	720	30	5	Ostium of left coronary artery narrowed	Cardiac failure	Marked
11	W	M	46	200/154	490	20	3	Anatomically patent foramen ovale	Cerebral hemorrhage	Moderate
12	C	M	66	250/160	775	25	7	Syphilitic aortitis	Cardiac failure, pernicious anemia	Slight
13	W	M	46	180/136	550	20	4	Fibrinous pericarditis	Cardiac failure	Slight
14	C	M	81	.....	590	20	5	.....	Cardiac failure	Slight
15	C	M	45	170/110	480	14	5	Very severe coronary sclerosis with complete occlusion of both arteries, thrombotic occlusion of left posterior cerebral artery	Severe coronary sclerosis, encephalomalacia from occlusion of left posterior cerebral artery	Marked
16	W	M	60	220/126	940	26	11	Subendocardial hemorrhages	Cardiac failure	Moderate
17	W	F	58	.....	645	21	5	Slight fibroplastic deformity of mitral and aortic valves	Cardiac failure	Slight
18	W	M	50	240/170	565	23	3	.....	Generalized peritonitis following resection of bowel	Slight
19	W	F	42	202/160	605	19	9	Slight fibroplastic deformity of mitral valve	Cardiac failure	Slight
20	C	F	42	242/138	735	20	6	.....	Cardiac failure	Slight
21	W	M	63	190/120	500	19	4	Hemorrhage in cerebellum.....	Cerebral hemorrhage	Marked
22	C	F	45	270/180	540	20	4	Malignant nephrosclerosis	Renal insufficiency (uremia)	Slight
23	C	M	65	115/ 85	590	16	6	Multiple anthracotic—silicotic nodules in lungs	Cardiac failure	Moderate
24	C	F	40	244/170	515	28	5	Malignant nephrosclerosis	Renal insufficiency (uremia)	Slight
25	W	M	54	165/ 60	740	22	8	Recent cortical encephalomalacia..	Cardiac failure	Moderate
26	W	F	63	140/ 90	700	18	4	Mural thrombus in left ventricle, fibrinopurulent pericarditis	Cardiac failure, small cortical fibrosarcoma of left kidney	Slight
27	C	M	48	184/112	615	20	4	Mural thrombi in left ventricle and right auricle, thrombi in pulmonary artery, prostatic abscesses with emboli	Cardiac failure, prostatic abscess with emboli	Slight

Findings in Twenty-Seven Hypertensive Hearts

Degree of Sclerosis of Medium-Sized Arteries Section							Degree of Sclerosis of Smallest Arteries and Arterioles							Amount of Scarring in Myocardium						
1	2	3	4	5	6	7														
Left Ventricle, Anterior Wall	Left Ventricle, Posterior Wall	Left Ventricle, Large Papillary Muscle	Intraventricular Septum Near Apex	Right Ventricle	Left Auricle	Right Auricle	Section 1	Section 2	Section 3	Section 4	Section 5	Section 6	Section 7	Section 1	Section 2	Section 3	Section 4	Section 5	Section 6	Section 7
0	0	0	+	trace	—	—	0	0	+	0	0	0	0	++	+++	+++	+++	0	0	trace
0	0	0	0	0	—	—	0	trace	+	trace	0	0	+	trace	+	+	+	trace	0	trace
trace	0	—	0	0	0	0	0	0	trace	0	0	0	0	trace	+	+	trace	trace	trace	+
0	0	0	0	0	—	—	0	0	trace	0	trace	trace	0	+	+	++	++	+	trace	+
0	0	—	+++	0	—	—	0	0	0	0	0	0	0	+	++++	++	+	++++	0	+++
0	0	trace	0	0	—	0	0	0	+++	0	0	0	0	trace	+	++	+	0	0	+
0	0	—	0	0	0	—	0	0	0	trace	0	0	+	0	trace	0	+	trace	0	+
0	0	—	0	0	—	—	0	0	+	0	0	0	trace	trace	++	++	+	0	+	+
0	trace	+	0	0	—	—	0	0	0	0	0	0	0	++	+++	+++	++	+	+	++
0	0	0	0	0	0	0	0	0	0	0	trace	0	0	trace	++	+	+	trace	+++	+
0	0	0	0	0	—	—	0	0	++	+	0	trace	trace	+	+	trace	+	+	+	+
0	0	0	0	0	0	—	0	0	0	++	0	0	0	++	+	++	++	++	0	++
0	0	0	0	0	—	—	0	0	0	0	0	0	0	trace	++	+	trace	+	0	trace
0	0	0	0	0	—	—	0	0	0	0	0	0	0	++	+++	+++	++	+	+	++
0	0	0	0	0	0	—	trace	0	0	0	0	0	0	++++	+++	+++	++++	+	0	+
0	0	0	0	0	—	0	0	0	0	0	0	0	0	+	++	+++	+	+	++	+
0	0	0	0	0	0	0	0	trace	+	0	0	0	0	++	+++	++	+	trace	++	++
trace	0	0	0	0	0	0	0	0	0	0	0	0	0	trace	+++	+	+	trace	0	0
0	0	0	0	0	0	—	0	0	+	0	0	0	0	+	++	+++	+	trace	+++	+++
0	0	0	+	0	0	0	0	0	trace	0	0	0	0	0	+	+	+	0	0	+
+	0	trace	0	0	0	—	0	0	++	0	0	0	0	+	+++	+	0	0	trace	+
0	0	trace	0	0	—	—	0	0	0	0	0	0	0	++	+	+++	+	+	+	trace
+	0	—	0	0	—	—	0	trace	+++	0	0	0	++++	++	+++	++++	++++	0	+	trace
0	0	0	0	0	—	—	0	0	0	0	0	0	0	+	+	+	++	0	0	+
0	0	0	0	0	0	—	0	0	++	0	0	0	0	+++	+++	+++	+++	+	+	+
0	0	0	0	0	—	—	0	0	0	0	0	0	0	0	++	+++	++	trace	0	++
0	0	0	0	0	—	—	0	0	trace	0	0	0	0	++	++	+++	++	+	++	+

the blood supply to have caused the myocardial fibrosis. The 13 cases in the category just cited overlap somewhat because the heart with marked sclerosis of the medium-sized arteries and 1 of the 6 with marked sclerosis of the arterioles also had marked sclerosis of the large coronary arteries. This leaves 11 hearts with marked anatomic changes in the arterial tree. In the remaining 16 cases the moderate

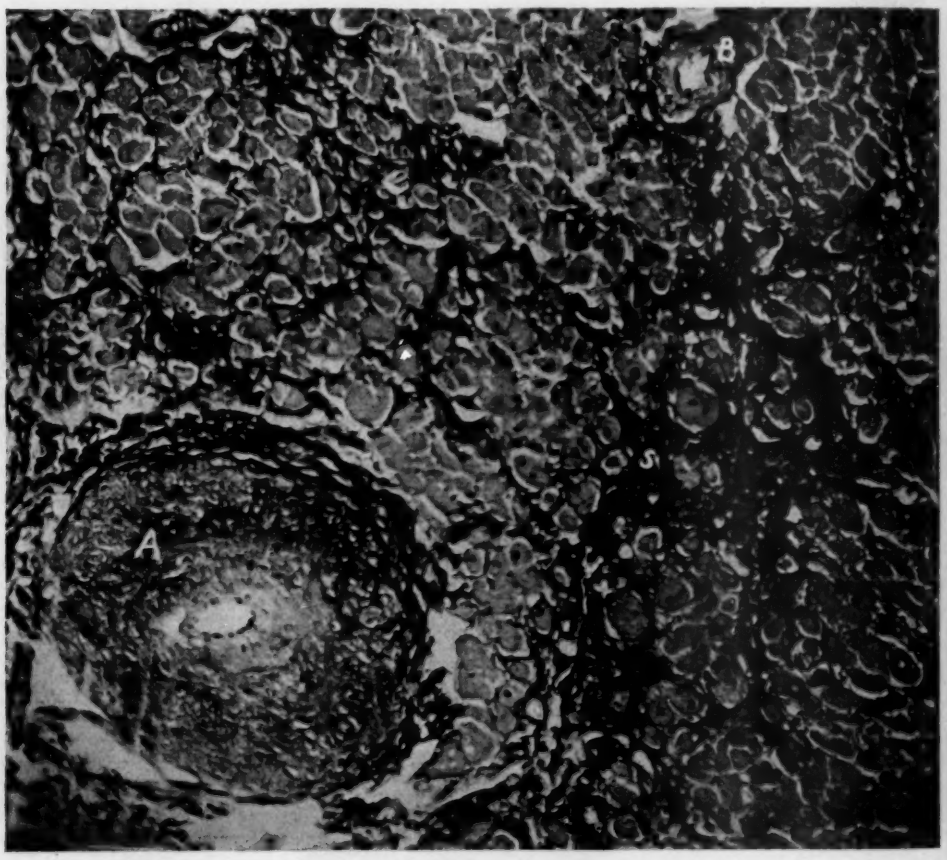

Fig. 1 (case 23).—Section showing diffuse scattered scarring in an area with marked arteriosclerosis (moderate sclerosis of the large coronary arteries). *A* indicates a much thickened arteriole; *B*, slightly thickened arteriole, and *S*, the scar. van Gieson's stain; × 150.

or slight changes in the large vessels and the amount of sclerosis in the smaller vessels (classed as one or two plus, at the most) were considered insufficient to have caused the microscopic fibrosis of the myocardium. The fibrosis in this second group must, then, be due to functional interference with the blood supply or to some other factor.

Other factors considered have been the weight of the heart, race, sex, age, blood pressure, the cause of death and the relation of the condition to syphilis. The hearts varied in weight from 475 to 940 Gm.; 3 weighed less than 500 Gm., 11 weighed between 500 and 600, 6 weighed from 600 to 700, 6 from 700 to 800 and 1 more than 900 Gm. The grouping of race and sex gives 10 white males, 9 colored males, 4

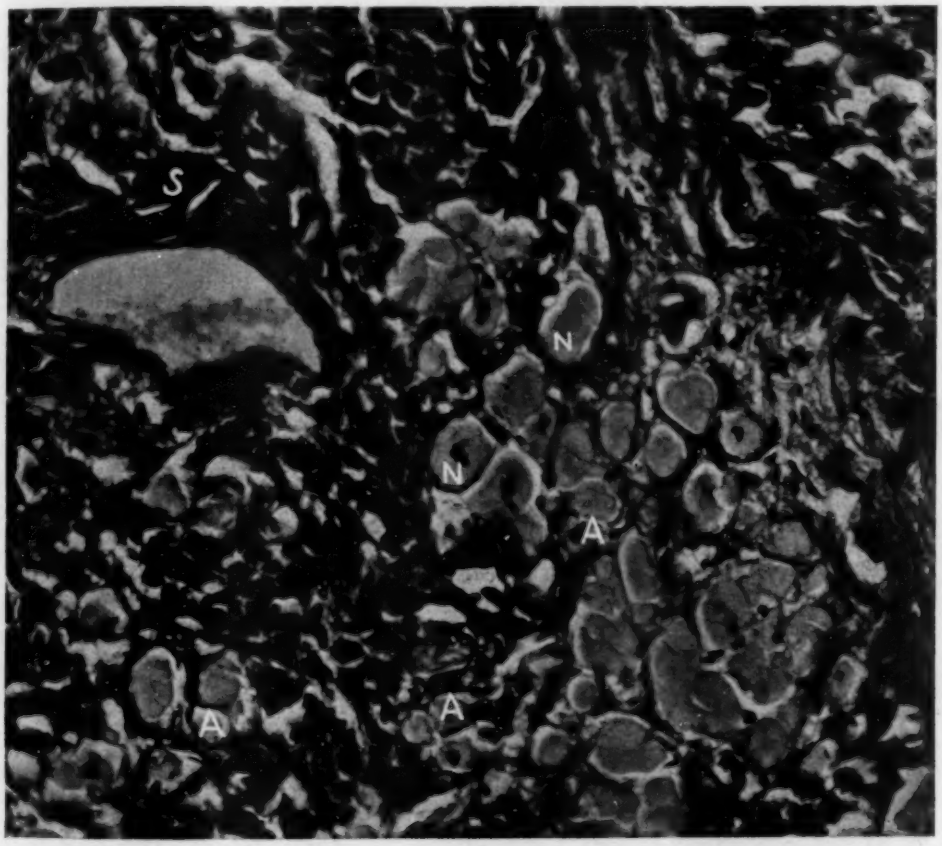

Fig. 2 (case 16).—Section showing a large interstitial scar. There was no arteriosclerosis or arteriolosclerosis in the heart. The scar tissue has surrounded and separated the muscle fibers and caused atrophy. *S* indicates the scar; N, normal-sized muscle fibers, and *A*, atrophic muscle fibers. van Gieson's stain; × 300.

white females and 4 colored females. The ages varied from 29 to 81, 1 patient being under 30, 9 between 30 and 40, 6 between 40 and 50, 7 between 50 and 60, 1 between 70 and 80, and 2 over 80. No correlation could be established between these factors and the myocardial fibrosis.

Dogliotti [15] and Miller and Perkins [16] recently showed that myocardial fibrosis does not develop as a result of advancing age. Thus the age of the patients could have no bearing on the amount of myocardial fibrosis present.

As to the blood pressure, in all but 2 of the cases (23 and 26) in which the blood pressure is given there was a definite hypertension. These 2 patients undoubtedly had a previous hypertension, since, as Willius and Smith [17] pointed out, hypertension may vanish, leaving only an enlarged heart.

With respect to the cause of death the cases can be divided into two main groups—19 cases in which death was due to cardiac failure and 7 in which it was due to other causes. The second group consists of 3 cases (7, 22 and 24) in which death was caused by renal insufficiency, 2 (11 and 21) in which it was due to accidents to the cerebral vessels, 1 (4) in which it resulted from ruptured dissecting aortic aneurysm and 1 (15) in which it was caused by occlusions of the cerebral and coronary arteries. In the remaining case (18) the patient died of peritonitis.

The factors of blood pressure and cause of death bore no noticeable relationship to the gross and microscopic observations. It is especially interesting, but not surprising, that no definite histologic change can be demonstrated after myocardial failure, since the shift from a state of compensation to one of decompensation is mainly an alteration of functional efficiency.

Syphilitic aortitis was present in only 3 cases (5, 6 and 12). No correlation can be demonstrated between the presence of syphilis and the amount of myocardial scarring present. Since the percentage of syphilis in this small series is approximately equal to the 10.3 per cent of syphilitic aortitis which Jaffé [18] found in 3,300 autopsies at the Cook County Hospital, it is reasonable to suppose that none of the other patients in my group had syphilis. For this reason the myocardial scars are not believed to have any relation to syphilis, and they are not similar to the syphilitic scars which Warthin [19] reported, because of the absence of any infiltrative phenomena in the region of the scars.

At this point it may be mentioned that stretching of the myocardium could not have caused the myocardial fibrosis, because the fibrosis was also observed in patients who had not died of decompensation of the heart, and because it was not the uniform, diffuse, perimuscular fibrosis that occurs with experimental dilatation of the ventricles.

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15. Dogliotti, G. C.: Ztschr. f. d. ges. Anat. (Abt. 1) **96**:680, 1931; Verhandl. d. anat. Gesellsch. **71**:14, 1931.

16. Miller, A. M., and Perkins, O. C.: Am. J. Anat. **39**:205, 1927.

17. Willius, F. A., and Smith, H. L.: Am. Heart J. **8**:170, 1932.

18. Jaffé, R. H.: Klin. Wchnschr. **10**:2081, 1931.

19. Warthin, A. S.: Proc. Inst. Med., Chicago **8**:173, 1931.

Endocardial sclerosis was also present in every heart. It is interesting that this sclerosis was, as a rule, most marked in the left auricle, the chamber which had the least amount of myocardial fibrosis. The most marked myocardial scarring was observed, on the other hand, in the left ventricle, especially in the posterior wall and the large anterior papillary muscle. The elastic tissue stain and van Gieson's stain revealed

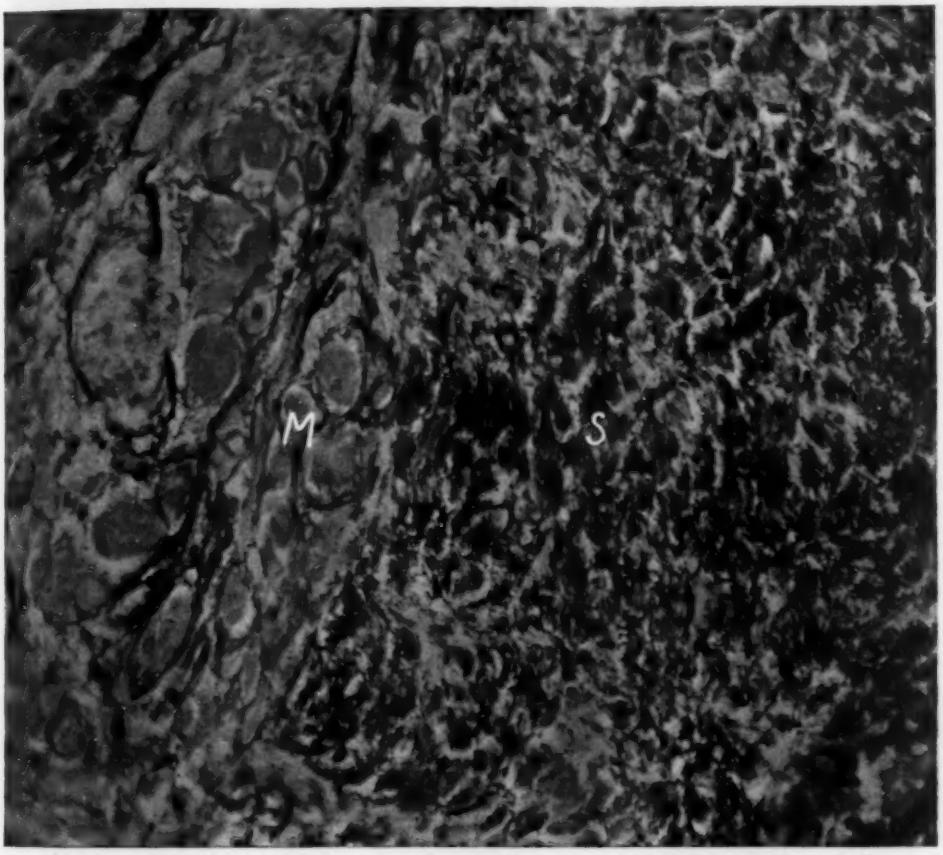

Fig. 3 (case 16).—Same scar as in figure 2, showing the large amount of elastic fibrils. *M* indicates the myocardium, and *S*, the scar. Weigert's elastic tissue stain; × 300.

that the endocardial thickening was due to an increase in the number of smooth muscle cells and elastic fibers normally present in the subendocardial layers. The elastic tissue stain also showed that the myocardial scars were composed of elastic fibrils varying from 30 to 100 per cent in various scars (fig. 3). As Perkins and Miller [20] pointed

20. Perkins, O. C., and Miller, A. M.: Arch. Path. **3**:785, 1927.

out, collagenic connective tissue can be converted into elastic connective tissue under the influence of stress and strain, contrary to the general notion that newly formed elastic tissue must be derived from preexisting elastic fibers.

COMMENT

Many recent studies on the hypertensive heart and fibrosis of the myocardium (Brown,[9] Cowan,[21] Barnes and Ball,[22] Burton and his collaborators,[23] and Gilchrist and Ritchie [24]) have failed to describe adequately the microscopic changes. Two recent articles, however, give microscopic observations in some detail. Clawson [13] studied a series of 139 hypertensive hearts, making microscopic examinations at five different places in each heart. These hearts were divided into four groups, in which death was due to severe coronary sclerosis, cardiac failure, cerebral hemorrhage or renal insufficiency. Clawson stated that the amount of myocardial fibrosis was proportional to the degree of coronary sclerosis. His figures showed that the hearts in the group in which death was due to coronary sclerosis had the most marked amount of myocardial fibrosis, but in the other groups the relationship was not proportional. Similarly, in my series, the most marked degree of myocardial fibrosis was present in the group with marked coronary sclerosis, but many hearts with only slight changes in the arterial tree had an amount of myocardial scarring equal to or greater than that in some of the hearts with marked coronary sclerosis.

Fitz Hugh [6] examined grossly and microscopically 228 hearts chosen on the basis of hypertrophy or fibrosis. Fourteen of these hearts he studied in great detail, making sections from six different locations. He concluded that while thick coronary arteries and marked myocardial fibrosis often occurred together, it was not unusual to find them present independently; the same was true as regards the relation of arteriolosclerosis and myocardial fibrosis. These views are thus contrary to those of Clawson. Mönckeberg,[25] too, in discussing fibrosis of the myocardium, stated that a definite parallelism between the grade of fibrosis and the severity of coronary sclerosis cannot be found.

Perkins and Miller,[20] studying a group of hypertensive hearts, observed changes similar to those in the group of 27 just described. They observed a much thickened endocardium, and many newly formed

21. Cowan, J.: Lancet **2**:1, 1930.

22. Barnes, A. R., and Ball, R. G.: Am. J. M. Sc. **183**:215, 1932.

23. Burton, J. A. G.; Cowan, J.; Kay, J. H.; Marshall, A. J.; Rennie, J. K.; Ramage, J. H., and Teacher, J. H.: Quart. J. Med. **23**:293, 1930.

24. Gilchrist, A. R., and Ritchie, W. T.: Quart. J. Med. **23**:273, 1930.

25. Mönckeberg, J. G.: Die Erkrankungen des Myokards und des specifischen Muskelsystems, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2.

elastic fibers and numerous scars throughout the myocardium. Their description of the scars as islands of connective tissue which enclosed fragments of degenerating muscle fibers exactly fits the picture seen in most of my sections. One obtains the impression that there has been a gradual shrinking of the muscle fibers, with replacement by fibrous tissue. Perkins and Miller believed that these scars were caused by a decreased nutritive supply. Decrease of the blood supply was also given by Cohn [5] as the cause of the scars which he described in the myocardium.

Other authors, too, have believed that an adequate or inadequate blood supply is the factor determining the myocardial changes. Miller and Weiss [26] studied diseases of the coronary arteries and concluded that adequate collateral circulation explained the lack of hypertrophy of the heart in the presence of coronary sclerosis. Jaffé and Bross [27] stated that the number of anastomoses between the coronary arteries and not the degree of occlusion determined the amount of myocardial damage. Christian [28] believed that hypertrophy of the heart often develops to such an extent that the capillaries cannot supply the muscle with sufficient blood, thus establishing a vicious cycle leading to decompensation and death.

Even in large macroscopic infarcts or areas of fibrosis it is not always possible to find definite occlusion of the large coronary arteries. Brown [9] found 25 hearts with normal coronary arteries among 110 hearts with gross fibrosis. In a series of 49 hearts with old infarcts, reported by Barnes and Ball,[22] many did not have complete coronary occlusion. Levine and Brown [29] reported 46 cases in which the heart showed large infarcts or infarct scars, and failed to find definite coronary occlusion in 11. Lisa and Ring [30] found normal coronary arteries in 8 hearts of a series of 100 with well circumscribed gross infarction or fibrosis. They could locate definite occlusion in only 57. Krumbhaar and Crowell [31] made an extensive report of spontaneous rupture of the heart and concluded that changes in the coronary arteries could not explain all cases of spontaneous rupture. Davenport [32] reported 52 cases of rupture of the left ventricle; he found changes in the coronary arteries in only 30. He concluded that more detailed

26. Miller, H. R., and Weiss, W. M.: Arch. Int. Med. **42**:74, 1928.

27. Jaffé, Rudolf, and Bross, K.: Centralbl. f. allg. Path. u. path. Anat. **56**: 246, 1933; Ztschr. f. klin. Med. **123**:63, 1933.

28. Christian, H. A.: South. M. J. **20**:28, 1927.

29. Levine, S. A., and Brown, C. L.: Medicine **8**:245, 1929.

30. Lisa, J. R., and Ring, A.: Arch. Int. Med. **50**:131, 1932.

31. Krumbhaar, E. B., and Crowell, C.: Am. J. M. Sc. **170**:828, 1925.

32. Davenport, A. B.: Am. J. M. Sc. **176**:62, 1928.

microscopic studies were necessary to arrive at any definite solution of this problem.

Such a careful study has recently been made by Jaffé and Bross.[27] These authors reported 9 cases in all, in 7 of which death was due to spontaneous rupture of the heart. In the first 2 cases the rupture occurred suddenly, the patients being in good health previously. The coronary vessels were smooth and unobstructed. In both these cases careful microscopic examination showed widespread changes both at, and some distance from, the rupture. These changes consisted of multiple focal areas of necrosis interspersed with areas containing marked engorgement of the capillaries. Jaffé and Bross concluded that functional disturbances in the terminal arterial tree led to the multiple areas of necrosis and the cardiac rupture.

In their next 3 cases the gross and microscopic observations were identical, but in addition in each instance there was an occluding thrombus in a branch of the coronary artery leading to the area of rupture. In the next 2 cases there was marked coronary sclerosis without definite occlusion. Yet all 5 of these hearts had the same microscopic areas of necrosis, leukodiapedesis and leukostasis present in their first 2 cases. These changes were much too diffuse and severe to have been accounted for by the condition observed in the coronary arteries, especially in the 3 hearts in which coronary occlusion was the only finding. In some areas older changes, such as fibrosis, were visible grossly and microscopically.

The last 2 hearts which Jaffé and Bross included in their series did not have a rupture. The first had an incomplete tear and marked coronary sclerosis. The second (their case 9) had widespread fibrosis, which was visible grossly, but no coronary changes. In both these hearts careful histologic study revealed numerous recent changes (necrosis, extravasation of leukocytes and stasis) similar to those in their first 7 cases, even in the areas of marked scarring.

In addition, Jaffé and Bross mentioned similar findings and observations of other investigators. Büchner[33] observed identical areas of myocardial necrosis in 5 grossly normal hearts from patients with angina pectoris. Oberndorfer[34] observed changes in the cardiac muscle in cases of angina pectoris similar to those in cases of sclerosis of the coronary arteries and believed their cause to be vascular spasm. Wollheim[35] reported a case in which the diagnosis was cardiac infarct and in which the only finding was subepicardial hemorrhage, due, he thought, to vascular spasm. Gruber and Lanz[36] found areas of "ischemic necrosis"

33. Büchner, F.: Beitr. z. path. Anat. u. z. allg. Path. **89**:644, 1932.
34. Oberndorfer: München. med. Wchnschr. **72**:1495, 1925.
35. Wollheim, E.: Deutsche med. Wchnschr. **57**:617, 1931.
36. Gruber, G. P., and Lanz, H. F.: Arch. f. Psychiat. **61**:98, 1920.

in a patient with epilepsy, and Neubürger [37] reported several cases of epilepsy in which the hearts had smooth coronary arteries and areas of "ischemic necrosis" of the myocardium, intermingled with scars. He attributed the changes to spasm of the vessels.

Other authors (Mönckeberg,[25] Levine and Brown,[29] Smith and Bartels [38] and Buckley [39]) noted similar myocardial changes, but failed to give them the same significance, usually considering them inflammatory. Jaffé and Bross [27] and Büchner [33] carefully examined large infarcts similar to those reported by Levine and Brown. Despite an obvious adjacent coronary occlusion they found that these infarcts were not uniform, as was suggested by their gross appearance, but were multiple, confluent small areas of necrosis.

In order to understand the underlying cause of the changes which Jaffé and Bross reported, it is necessary to refer to the studies of Ricker [40] and his school. Briefly stated, Ricker found that the blood vessels react in segments to stimuli brought to them, each segment being a functional unit. The large vessels react differently from the medium-sized ones and from the smallest vessels (small arteries, arterioles and capillaries, which form a functional unit). The terminal vascular segments (which Ricker believed to receive a great number of nervous impulses) react to weak irritation by vasodilatation, to medium irritation by vasoconstriction and to strong irritation by marked vasodilatation and slowing of the blood stream, while the proximal arterial segments remain constricted. This is the state which Ricker calls "peristasis" (inflammatory hyperemia), which leads without sharp demarcation to "prestasis" (vasoparesis) and, in the last degree, to stagnation of the blood stream, or "stasis" (vasoparalysis). Peristasis causes exudation of serum and leukocytes; prestasis causes irregularity in the blood contents and diapedesis of erythrocytes, and stasis causes stoppage of blood flow and conglutination of red blood cells, which are no longer individually recognizable.

According to Ricker, in the earlier stages the terminal arterioles may be constricted, while the capillaries become dilated. Thus the blood stream has a lessened *vis a tergo* and becomes slowed in the capillaries. Later the arterioles dilate, while the more proximal arterial segments remain constricted, resulting in a similar slowing of the blood stream in the arterioles. This leads to the changes mentioned and finally ends in stoppage of the blood stream in stasis. Even when stasis is reached

37. Neubürger, K.: Verhandl. d. deutsch. path. Gesellsch. **23**:487, 1928; Klin. Wchnschr. **12**:1355, 1933.

38. Smith, H. L., and Bartels, E. C.: M. Clin. North America **15**:1585, 1932.

39. Buckley, R. C.: Am. J. Path. **4**:249, 1928.

40. Ricker, G.: Pathologie als Naturwissenschaft- Relationspathologie, Berlin, Julius Springer, 1924.

the process is not irreversible, and a return to normal is possible if the exciting factor, i. e., the nervous stimulus, is removed. Also, this sequence of events is not always carried through gradually in all its stages, but its speed may vary considerably at any one stage. Necrosis may and frequently does follow stasis, when the stasis persists and becomes permanent. Ricker stated that necrosis may follow either organic blocking of a vessel or stasis, each of which severs the connection between part of an organ and the blood stream.

According to Jaffé and Bross, Ricker's views, which are supported by his experimental work and partly by that of Tannenberg,[41] explain the microscopic observations of necrosis, leukodiapedesis and stasis in their series of hearts and in the cases which they cited. They advanced the suggestion that thinning over an occluded point or dilatation of the coronary artery ahead of an occlusion may send the stimuli to the terminal vessels and lead to the changes described. When there is no occlusion they believe that spasm of a large artery may supply the needed stimulus. Thus, Jaffé and Bross believe that the widespread small necrotic changes are not "ischemic" but "static."

It must be mentioned, however, that not all recent investigators agree entirely with Ricker. Fischer-Wasels,[42] in a recent review of the subject, came to the conclusion that a toxic factor must also be present to cause necrosis. Peissachowitsch [43] recently disproved some of Ricker's ideas but not his underlying thesis.

Pathologic alterations of other organs have also been explained on the basis of Ricker's theory. Shapiro [44] applied the theory to the changes in the kidneys in malignant nephrosclerosis. Scriver and Oertel [45] and Wolfson [46] used it to explain bilateral cortical necrosis of the kidneys in pregnancy, and Ricker [40] and his associates explained various pathologic conditions on the basis of functional vascular disturbances.

As Neubürger [37] and Jaffé and Bross [27] (especially in their case 9) pointed out, the late severe necrotic changes may be intermingled with older interstitial areas of fibrosis. It is easily conceivable that in some hearts only the fibrosis may be present, owing to the slower development or minor severity of the circulatory disturbances.

This seems to hold true for the 16 hearts without organic vascular changes in my series of 27 hypertrophic hearts. All 16 had scattered microscopic areas of fibrosis. The microscopic picture of the areas gives

41. Tannenberg, J.: Frankfurt. Ztschr. f. Path. **31**:173, 1925.
42. Fischer-Wasels, B.: Frankfurt. Ztschr. f. Path. **45**:1, 1933.
43. Peissachowitsch, K.: Frankfurt. Ztschr. f. Path. **45**:246, 1933.
44. Shapiro, P. F.: Arch. Int. Med. **48**:199, 1931.
45. Scriver, W. de M., and Oertel, H.: J. Path. & Bact. **33**:1071, 1930.
46. Wolfson, A.: Tr. Chicago Path. Soc. **14**:33, 1932; personal communication to the author.

one the impression that there has been a gradual melting away of the muscle fibers without acute necrosis (which would be the change in the analogous rapid process) and a gradual replacement of this disappearing muscle tissue by scar tissue.

The observations for these hearts are comparable to those in benign nephrosclerosis, and the observations in case 9 of Jaffé and Bross resemble those in severe rapidly developing necrotic lesions of malignant nephrosclerosis engrafted on the changes of benign arteriolosclerosis of the kidneys. The changes in the first 2 cases which Jaffé and Bross reported are analogous to those in malignant nephrosclerosis without any preexisting benign sclerotic vascular changes. In my series 11 hearts had organic vascular changes which, by interfering with the blood supply, might account for the scarring, but which, in accordance with the statement of Jaffé and Bross, may also have been due, at least in part, to spasm and later paralysis of the terminal arterial segments.

SUMMARY

Twenty-seven hypertensive hearts were examined grossly and microscopically. For the microscopic examination blocks of tissue were taken from seven different locations in each heart.

Six hearts were found to have marked sclerosis of the large coronary arteries. Six hearts had a marked sclerosis of the arterioles in one or more sections. Since 1 of the 6 with marked arteriolosclerosis also had marked sclerosis of the large coronary arteries, there were 11 hearts which had marked organic changes in the arterial tree. The remaining 16 hearts had changes in the arterial tree which were considered too slight to have seriously interfered with the blood supply.

In all the hearts minute myocardial scars were observed in many areas. As a rule, this fibrosis was most marked in the left ventricle. The most marked scarring was present in the hearts with marked alteration of the wall of the arteries and arterioles, but many hearts in the group without organic arterial changes also had marked interstitial fibrosis.

No correlation could be found between age, sex, race, weight of the heart, blood pressure, the cause of death or the presence of syphilis and the amount of myocardial fibrosis. Many of the scars in the myocardium were observed to contain varying amounts of elastic tissue. This bears out the contention of Perkins and Miller that stress and strain can convert collagenic connective tissue into elastic tissue.

Endocardial sclerosis was present in all the hearts, being as a rule, most marked in the left auricle. It was usually due to an increase in smooth muscle cells and elastic fibers.

Failing to find an anatomic basis for the myocardial fibrosis present in the 16 hearts without organic changes in the arterial tree, one is forced to rely on an explanation of functional disturbances. The views of Ricker on functional spasm and later vasoparalysis of the terminal arterioles, interpreted in the light of the work of Jaffé and Bross, appear to give a logical solution of the question. In these 16 hearts the functional changes undoubtedly acted over a long period and in a mild degree, leading only to myocardial fibrosis.

BILATERAL GLIOBLASTOMA MULTIFORME

REPORT OF TWO CASES

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A glioblastoma multiforme which extends across the midline to involve adjacent brain tissue of the opposite hemisphere is not particularly rare.[1] However, glioblastoma multiforme appearing in widely separated centers in the two hemispheres is quite unusual.[2] Because of this fact the following report of two cases presenting that condition seems warranted.

The cases studied appeared in a series of forty autopsies on patients with tumors of the brain. They represent the only bilateral growths in this series with the exception of one case of bilateral perineural fibroblastoma of the auditory nerves.

When first studied both were thought to be cases of bilateral glioblastoma multiforme of multicentric origin. A careful study of sections proved that in case 1 the growth was an extension from the left temporal to the right parietal cortex. It was represented only by a fine filamentous tumor tissue near the midline. In case 2 the tumor is considered a bilateral tumor of multicentric origin. No communication whatever could be demonstrated between the two growths, and each appeared as a separate, well defined tumor.

The possibility of one of these growths (case 2) being a metastasis from the other cannot be entirely ruled out since each growth came into contact with a small area of the arachnoid. Also, the right tumor formed a portion of the wall of the right ventricle, thus predisposing to metastasis.[3] While this possibility is fully admitted, it is not considered the most likely explanation because of the character of these two lesions. Each tumor appeared as a separate entity with no metastases or extensions into the subarachnoid space.

An interesting feature is the fact that in each case one tumor conformed quite closely to the "typical" glioblastoma multiforme,[4] while

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From the Department of Bacteriology and Pathology, Indiana University School of Medicine, aided by a grant from the Research Division.

1. Bailey, Percival: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

2. Hosoi, K.: Arch. Neurol. & Psychiat. **24**:311, 1930. Penfield, Wilder: Personal communication to the author.

3. Cairns, H., and Russel, D. S.: Brain **54**:377, 1931.

4. Deery, E. M.: Bull. Neurol. Inst. New York **2**:157, 1932.

that of the opposite hemisphere was distinctly of the "astrocyte type" of glioblastoma multiforme.

No attempt has been made to correlate these cases with multiple gliomas previously reported. Such a summary may be left until more complete records are available and more uniform methods and terminology come into general use.

REPORT OF CASES

CASE 1.—A white man, aged 48, entered the Robert W. Long Hospital on Sept. 26, 1932, complaining of frontal and occipital headaches of four months' duration. The headaches had become quite severe during the latter months of his illness and were most intense in the right occipital region, radiating to the vertex. Occasional vomiting became a feature of the illness two weeks before death. Pertinent physical findings included impairment of memory, bilateral optic edema and a spinal fluid pressure of 20 mm. of mercury with a normal Queckenstedt sign. The left biceps, triceps and ankle jerks were absent. On the right the deep reflexes and the left knee jerk were normal. There was no alteration in muscular strength or cutaneous sensation. A diagnosis of right parietal tumor of the brain was made. A right parietal decompression was done, and an inoperable tumor was found. The patient died thirteen days after the operation.

Gross and Microscopic Examination of the Brain.—The meningeal vessels were moderately injected and the convolutions flattened. The ventricles were dilated, and a few small cysts (1 or 2 mm.) were found in the choroid plexus of the right ventricle. There was no evidence of metastasis other than that to be described.

Left Hemisphere (fig. 1): Over the left posterior part of the temporal lobe, just below the superior temporal sulcus, was a large area of purplish-brown cortex. This consisted in the outer portion of a soft, degenerated, brownish tumor, measuring 3 by 4 by 7 cm. The cortex was involved to a lesser extent than the subcortex. The tumor contained numerous small hemorrhages, and its margins were indefinite with no attempt at encapsulation. The growth extended to the posterior horn of the lateral ventricle where it made up a sizable portion of the wall of that structure. From the left lateral ventricle the tumor appeared to extend medially by a thin pedicle growth. This continued behind the splenium of the corpus callosum across the midline and into the right hemisphere. There it formed the lesion on the right side, to be described.

Microscopic Examination: The tumor consisted of a vascular and cellular tissue. The vessels presented an endothelial and adventitial overgrowth, of which the latter was more prominent. Neuro-ectodermal cells were numerous and were found in clumps and also diffusely distributed throughout the section. They joined with the spongioblasts to form a pseudopalisade about many degenerating and necrotic areas. The spongioblasts were mostly of the apolar type and were well demonstrated with phosphotungstic acid and hematoxylin. A few multinucleated giant cells were noted, and mitotic figures were not infrequent. Many astrocytes fringed the tumor tissue. When stained with gold chloride these showed varying degrees of degeneration. Only comparatively few astrocytes were found in the tumor itself. This was made up principally of spongioblasts and neuro-ectodermal cells as stated.

The diagnosis was glioblastoma multiforme of the left temporal lobe.

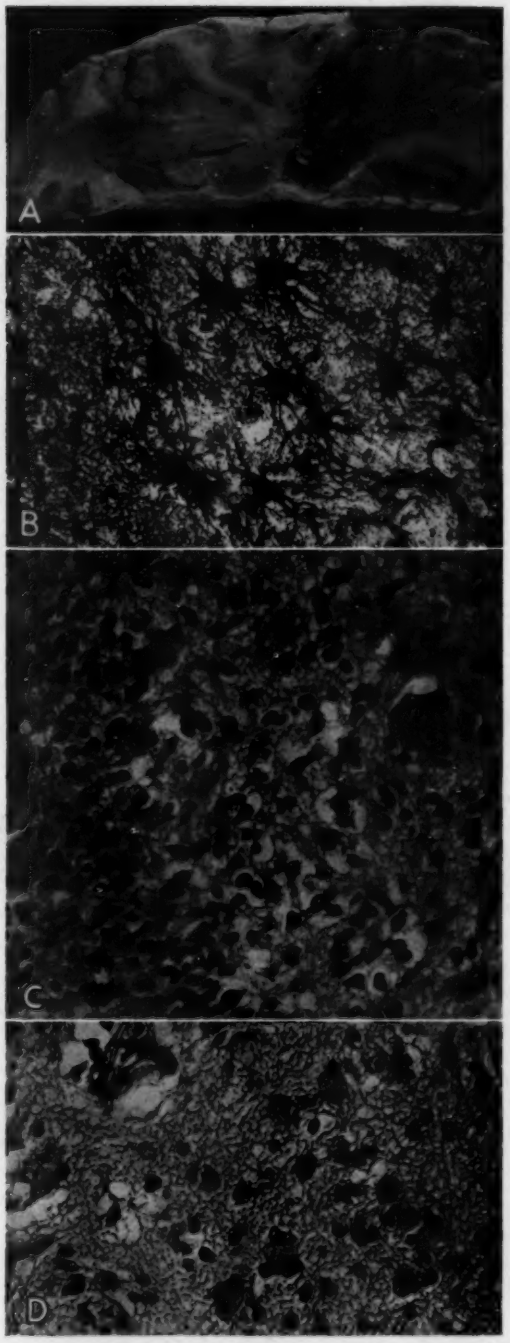

Fig. 1 (case 1).—*A*, tumor of the left temporal lobe forming part of the left lateral ventricle indicated by the arrow; *B*, varying degrees of astrocyte degeneration fringing the neoplasm (gold chloride); *C*, general structure, slight palisading, occasional mitotic figures and adventitial proliferation (hematoxylin and eosin); *D*, area of tumor containing many astrocytes (phosphotungstic acid and hematoxylin). Reduced from × 450 and × 300.

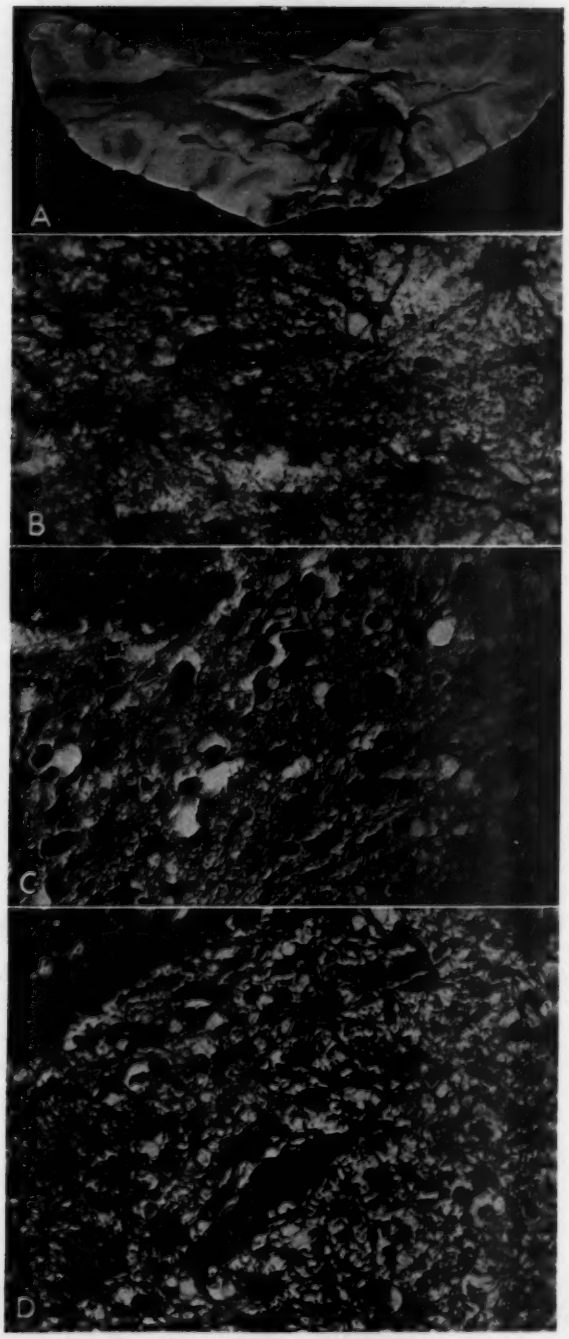

Fig. 2 (case 1).—*A*, right parietotemporal tumor; *B*, degenerating astrocytes in the marginal zone (gold chloride); *C*, representative area made up largely of astrocytes (hematoxylin and eosin); *D*, astrocytes, spongioblasts and neuroectodermal cells in the subarachnoid space. Sucker feet attached to the thickened vessel wall are poorly shown (phosphotungstic acid and hematoxylin). Reduced from × 450 and × 300.

Right Hemisphere (fig. 2): In the parietotemporal region just posterior to the postcentral gyrus was a cortical area of degeneration and hemorrhage. This measured 3 cm. in diameter and was roughly pyramidal in shape (fig. 2). The apex extended medially around the ventricle to join the previously noted small pedicle of tumor tissue from the opposite hemisphere. Grossly and microscopically the tumor did not involve the right ventricle, although at one point the wall of the ventricle was partially necrotic. The bulk of the tumor was deep in the white matter and peripherally involved the sulci, leaving several of the gyri relatively intact (fig. 2). The tumor tissue was much more firm and limited than that of the opposite side. Degeneration was less on the right, though there were numerous hemorrhages.

Microscopic Examination: Sections of the tumor tissue showed it to be invading the subarachnoid space. In contradistinction to the opposite side, the astrocytes were numerous and prominent while there were fewer spongioblasts. Occasional multinuclear giant cells were found, and there were a few mitotic figures. There were many neuro-ectodermal cells scattered throughout the section, and clumps of them were found around degenerating areas. Portions of the tumor had a loose structure with the predominance of astrocytes suggesting an astrocytoma. The most striking feature of the tissue was the extreme thickening of the walls of the numerous blood vessels. This consisted for the most part of an endothelial proliferation, but hyperplasia of the adventitia was also found. Some of the vessels were completely occluded by the process. Section through the right ventricle showed the wall of that structure to be involved by the tumor.

The diagnosis was glioblastoma multiforme of the right parietal cortex by direct extension from the glioblastoma multiforme of the left temporal lobe.

Comment.—This case was considered one of multiple glioma in which the tumor of the left temporal region was primary. This neoplasm, glioblastoma multiforme, extended by a thin filamentous growth across the midline into the right parietal cortex where a second similar neoplasm was produced.

CASE 2.—An American housewife, aged 41, entered the Robert W. Long Hospital on June 21, 1933, complaining of drowsiness of three weeks' duration. Her lethargy had been slowly but steadily increasing, and on admission she could be aroused only with difficulty. Since the onset the patient had eaten but little, and constipation had been quite severe. A routine physical examination revealed only slightly hyperactive ankle and biceps reflexes. These were equal for the right and left sides. The pupils were sluggish but reacted equally to the light stimulus. The laboratory examinations showed a white cell count of 12,000 with 90 per cent polymorphonuclears. The blood sugar, total nonprotein nitrogen and red cell count were within normal limits. The urine was loaded with pus cells, and for this reason immediate attention was focused on clearing up a rather severe pyelitis. Occasional coarse tremors of the arms and legs were noted after admission. The patient died suddenly on the first day after entering the hospital before a neurologic study could be made.

Gross and Microscopic Examination of the Brain (fig. 3).—The vessels over the vertex were engorged and prominent. There was no dilatation of the ventricles. The convolutions of the cortex were slightly flattened, and there was a soft cystic mass in the right frontal lobe. Dissection of the frontal lobes revealed the following picture:

Right Frontal Lobe: In the anterior medial portion of the right frontal lobe was a large soft area which measured 3 by 3 by 5 cm. This extended from the

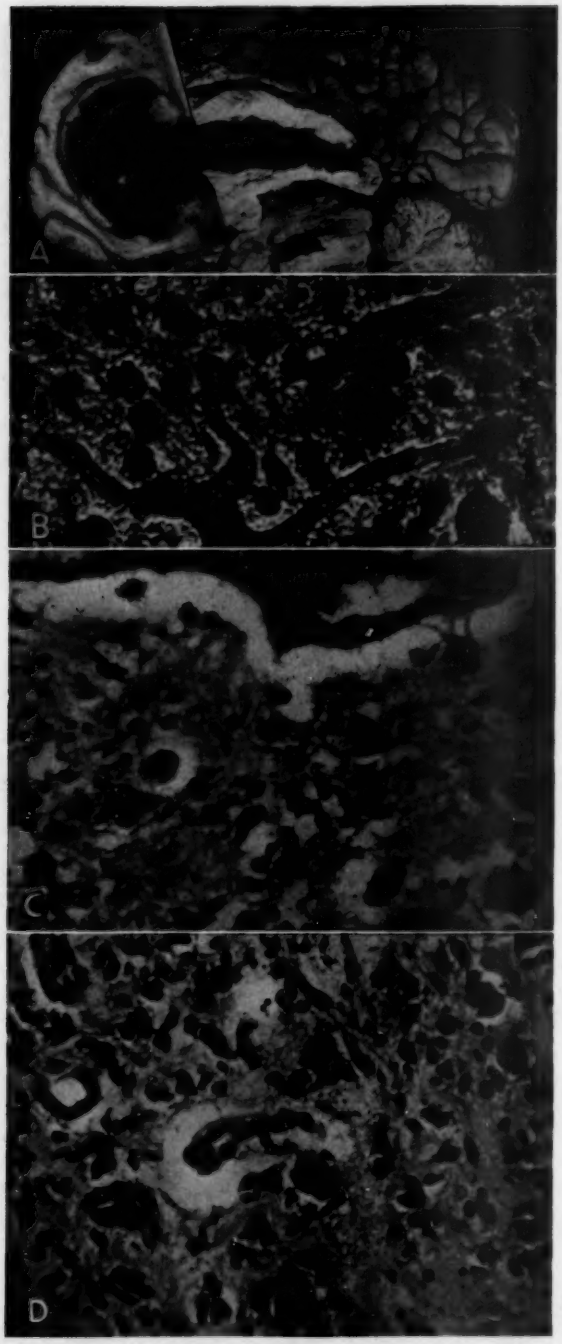

Fig. 3 (case 2).—*A*, invasive tumor of the right frontal lobe reaching the lateral ventricle and a small area of the meninges; *B*, spongioblasts (gold chloride); *C*, thickened vascular walls, hyperchromatic multinucleated cells, mitosis, spongioblasts and neuro-ectodermal cells (hematoxylin and eosin); *D*, same picture with phosphotungstic acid and hematoxylin stain. Reduced from × 450.

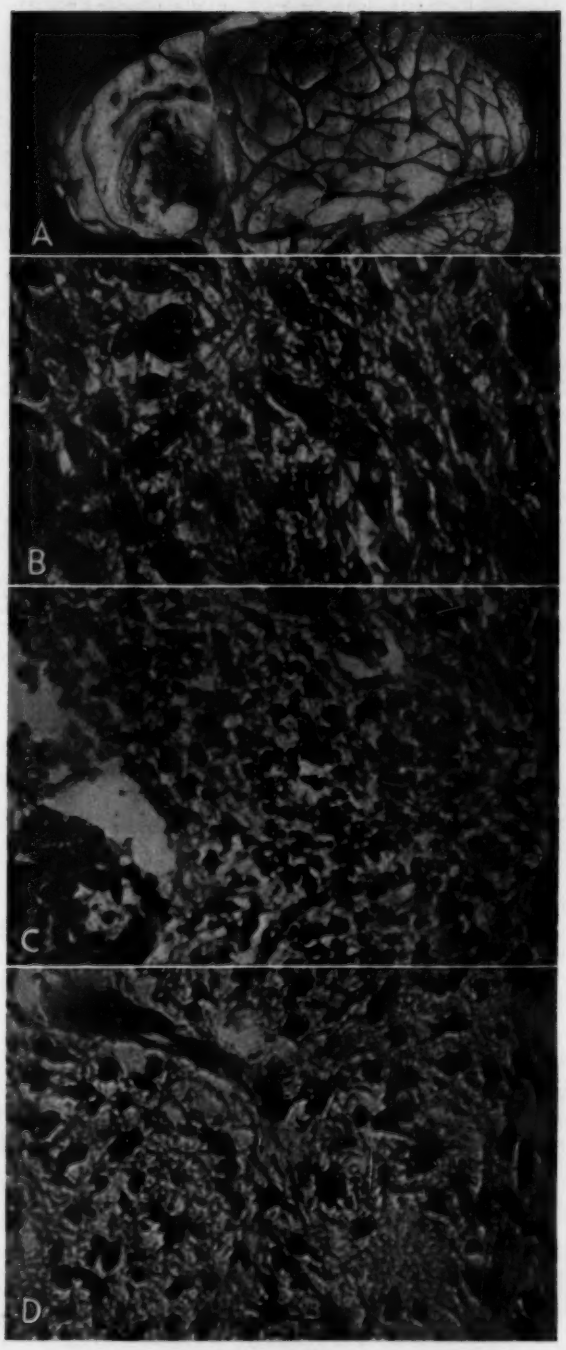

Fig. 4 (case 2).—*A*, tumor of the left frontal lobe; *B*, polar spongioblasts and astrocytes showing glia fibrils (phosphotungstic acid and hematoxylin); *C* and *D*, astrocytes, spongioblasts and neuro-ectodermal cells (hematoxylin and eosin). Reduced from × 450 and × 300.

medial surface of the frontal cortex laterally to surround and encroach on the anterior horn of the lateral ventricle. The entire tumor lay beneath the cortex except where it came to the surface at one point on the medial surface of the lobe. The tumor itself was soft and necrotic. It contained numerous large and small hemorrhages. Areas of necrosis were present which contained many small yellowish-gray particles. The mass appeared quite invasive and showed no tendency to encapsulation. It was considerably less circumscribed than the tumor on the opposite side but was definitely confined to the right frontal lobe.

On microscopic examination the sections presented a "typical" glioblastoma multiforme with great variations in the size and shape of its constituent cells. Many hyperchromatic multinucleated giant cells were scattered throughout the tissue. Mitotic figures were numerous (from one to two per high power field). Many of these were quite bizarre. Apolar spongioblasts and neuro-ectodermal cells constituted the majority of the cells present. There were many variations in the size and shape of these elements, and they were scattered irregularly without any architectural pattern. The presence of astrocytes was not a prominent feature except in a few less cellular areas where they were quite numerous. In those areas the tissue suggested an astrocytoma. Occasional areas of necrosis and free hemorrhage were noted. The tumor tissue was quite vascular. Many of the smaller blood vessels showed both endothelial and adventitial thickening causing partial occlusion of their lumens.

The diagnosis was glioblastoma multiforme of the right frontal lobe.

Left Frontal Lobe (fig. 4): In the region of the inferior frontal sulcus was a hard firm tumor mass which measured 1.5 by 3 by 4 cm. It barely reached the lateral cortex and did not extend medially as far as the lateral ventricle. The tumor tissue was grayish yellow and rather uniform except for some necrosis about its margins. In some areas the tumor had a tendency to follow along the sulci rather than to destroy all the tissue to the same degree. Little hemorrhage or necrosis was present. There was no encapsulation, and the mass was not sharply circumscribed. No connection could be demonstrated between this tumor and the one in the opposite frontal lobe.

Microscopic examination showed polar spongioblasts predominating in this tissue. These formed wide interlacing bundles. Astrocytes were numerous and formed large fields of tissue which were identical with those of an astrocytoma. In other areas astrocytes were comparatively rare, and many neuro-ectodermal cells were found. Multinucleated giant cells and mitotic figures were not frequent. A few large and small areas of necrosis and hemorrhage were noted. Some of these were fringed by a pseudopalisading of spongioblasts and neuro-ectodermal cells. The tumor was quite vascular, and many of the walls of its blood vessels were greatly thickened. This was the result of endothelial and adventitial overgrowth. In some instances the lumen of the vessel was practically obliterated.

The diagnosis was glioblastoma multiforme of the left frontal lobe.

Comment.—This case is considered one in which a glioblastoma multiforme appeared independently in the right and left frontal lobes. A careful study of sections revealed no continuity between the two growths. There was no other evidence of metastasis. However, the possibility of one growth appearing as a metastasis from the other cannot be ruled out entirely since both tumors extended to the meninges. The part of the left tumor enclosed by an area of pia-arachnoid measured only a few millimeters in diameter.

The fibrillary elements of the tumor of the left lobe were more prominent than those of the opposite side, and in many large areas they had the appearance of an astrocytoma.

SUMMARY

Two cases of bilateral glioblastoma multiforme are reported.

In case 1 tumors of the left temporal and right parietal lobes were found joined by a filamentous strand of tumor tissue. This passed from one hemisphere to the other just posterior to the splenium of the corpus callosum. It was thought that the left temporal tumor was primary and produced a similar lesion in the right parietal cortex by direct extension into the opposite hemisphere.

In case 2 the tumor was believed to be a bilateral glioblastoma multiforme of the frontal lobe of multicentric origin. No communication or extensions could be demonstrated. It is freely admitted that the possibility of metastasis from one frontal lobe to the other cannot be entirely ruled out since the pia-arachnoid bounded a small portion of each growth. There was, however, no other suggestion of metastasis in the brain.

CHANGES IN THE BRAIN IN PERNICIOUS ANEMIA

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Changes in the brain associated with pernicious anemia are uncommon, in contrast to those in the spinal cord, which have been well studied. Only a few cases have been reported in which the changes in the brain corresponded histologically with those in subacute combined degeneration of the cord (Preobrazhenski,[1] Lurie,[2] Woltman,[3] Weimann[4] and others).

Lurie studied four cases of pernicious anemia, all of which showed mental symptoms long before death. In three he found in the brain foci of Lichtheim's type and of Preobrazhenski's miliary foci, aside from typical lesions in the spinal cord.

Woltman, from his study of seven cases of pernicious anemia with changes in the cord and brain, came to the conclusion that lesions in the brain run fairly parallel to those of the cord and occur with about the same frequency. Only one patient exhibited mental symptoms, which, however, predominated in Weimann's cases; in one patient they lasted four years and terminated in death.

Both Lurie and Weimann claimed that in the center of the degenerated areas they invariably found a blood vessel, while, according to Woltman, the foci "may or may not be connected with blood vessels."

Of seven cases with a typical picture of subacute combined degeneration of the cord in which the brain was available for study, only one revealed equally typical changes in the brain. Two showed minor changes, such as swollen oligodendroglia, rarefactions, numerous astrocytes and scattered vacuolated areas of minute size. Most of the last-mentioned areas were devoid of cell contents; some harbored glia nuclei. As these changes are often present in other pathologic conditions of the brain, they were not considered significant. Four cases showed no changes in the brain, nor did the patients present mental or cerebral symptoms, except terminal mental disturbances (confusion, hallucinations and stupor).

From the Division of Neuropathology of the University of Illinois College of Medicine; Dr. G. B. Hassin, Director.

1. Preobrazhenski, P. A.: Neurol. Centralbl. **21**:727, 1902.
2. Lurie, L. A.: Arch. Neurol. & Psychiat. **2**:67, 1919.
3. Woltman, H. W.: Arch. Int. Med. **21**:791, 1918.
4. Weimann, W.: Ztschr. f. d. ges. Neurol. u. Psychiat. **92**:433, 1924.

Of these seven cases one is reported, with a description of the changes in the brain; the changes in the spinal cord in this case have been thoroughly discussed by Hassin,[5] who purposely omitted the description of the cerebral lesions, as they were considered striking enough to warrant a separate study.

REPORT OF CASE

History.—The patient, aged 45, was admitted to the neurologic service of the Cook County Hospital because of difficulty in walking, cramps in the big toes, tingling, reeling gait and "electric shocks" running down his spine. The duration of the illness had been two years.

Examination and Course.—He had a spastic gait, an exaggerated patellar reflex, absence of the achilles reflex and positive Babinski, Rossolimo, Chaddock and similar signs. The cranial nerves, pupils and fundi were normal. The position sense was lost, and the vibratory sense was impaired in the lower extremities.

The number of red blood cells was greatly diminished; the hemoglobin ranged from 65 to 80 per cent, and the color index was 1.2. Differential white and red blood cell counts showed no abnormal forms. Analysis of the stomach revealed achylia gastrica.

The patient grew progressively worse. Atrophy of the right leg and anesthesia below the spine became more evident; incontinence of the bladder set in, and paraplegia in flexion developed. A few days before death from bronchopneumonia he became stuporous and drowsy and was hard to arouse.

The spinal cord presented a typical picture of subacute combined degeneration. The brain revealed no changes macroscopically.

Microscopic Changes.—Numerous and extensive foci of degeneration (status spongiosus) were scattered in the motor area (fig. 1). On closer examination these areas were found to consist of numerous gliogenous formations (fig. 2), some of which contained basophilic metachromatic granules; others were myelophages or gitter cells α, but the majority were the classic gitter cells β. Aside from the myelophages and the various gitter cells, numerous cytoplasmic astrocytes were present, which were especially massed around the blood vessels where they formed a wall along the pia glial membrane. The areas of the adjacent spaces of the adventitia were filled with gitter cells, while adventitial elements frequently harbored droplets of fat. The foci were mostly devoid of blood vessels, and only one focus had a blood vessel running through its center. The ganglion cells were somewhat swollen; some exhibited chromatolysis and neuronophagia, but in general the changes in the gray matter were much less marked than in the white matter.

The Bielschowsky and Alzheimer-Mann staining methods revealed in the affected areas, but somewhat remote from the actual foci of softening, rows of vacuoles that contained fragments of swollen axons and myelin, Marchi globules and few myeloclasts. Some of the vacuoles were encircled by a ring emanating from the glia nucleus. In these areas myelophages could be discerned, that is, nerve degeneration was here more advanced, but was fully developed in the areas of status spongiosus just described. Careful study of other cortical areas, of the corpus striatum and the optic thalamus revealed no changes. Few vacuoles of minute, miliary size could be seen in the pons.

5. Hassin, G. B.: Arch. Neurol. & Psychiat. **29**:855, 1933.

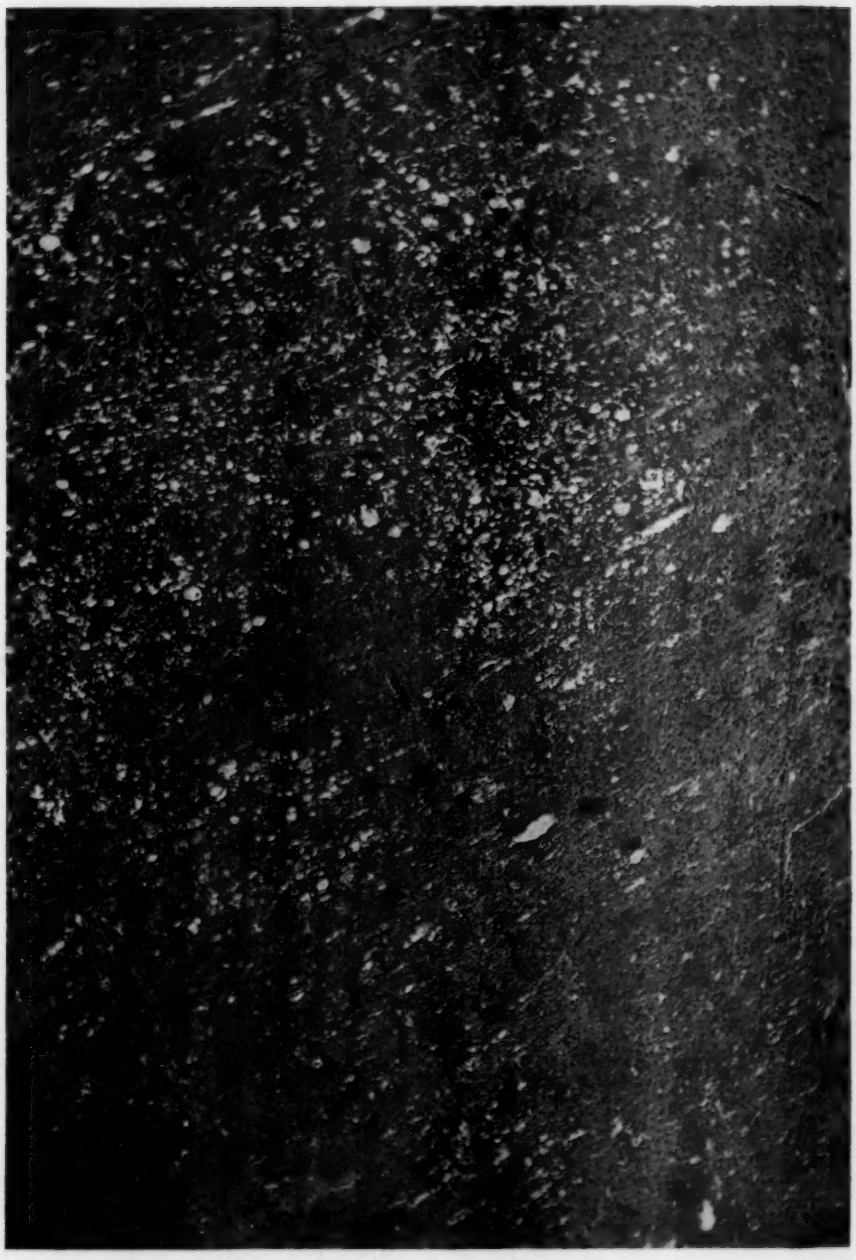

Fig. 1.—Large focus of degeneration in the subcortex of the frontal lobe (status spongiosus); the cortex itself is not involved; Alzheimer-Mann stain.

In the cerebellum the molecular layer and the granular cell layer showed fissures in some sections. These were near the pia mater and contained round, homogeneous, pale bodies (amyloid bodies), some of which were enveloped by delicate fibers of glia. In other places the fissures contained red and other blood cells. Aside from the fissures, there were reactive phenomena in the surrounding glia tissue in the form of fibrillary and cytoplasmic astrocytes. The Purkinje cells, as well as the processes, were tumefied and densely stained.

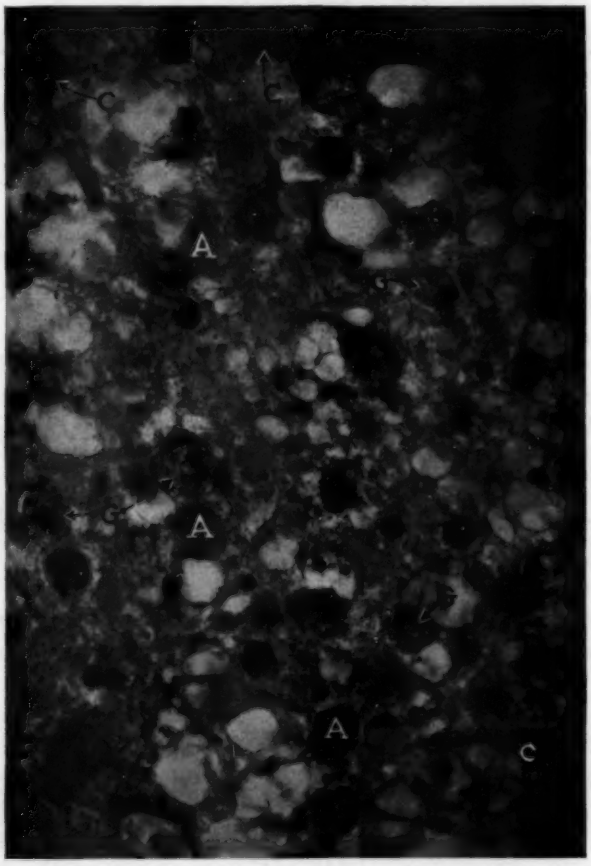

Fig. 2.—Higher power magnification of figure 1; numerous gitter cells (*G*) are interspersed with astrocytes (*C*) and amyloid bodies (*A*); Alzheimer-Mann stain.

The changes in the subarachnoid space were those of so-called aseptic meningitis. The pia-arachnoid was thickened; the meshes contained many small and large lymphocytes, mesothelial cells and numerous gitter cells. In one area there were numerous blue granules, appearing partly as conglomerations and partly within large, nucleated cells. The nature of these could not be ascertained. Probably they were particles of fatlike substances.

The tuft cells of the choroid plexus were swollen; some contained vacuoles, while others were granular. The granules, when stained with toluidine blue, appeared as bluish, dustlike grains of sand scattered over the cytoplasm; other granules appeared as droplets and stained darker. Some such granules, which are often seen in tuft cells of the choroid plexus, stain red with scarlet red and blue with thionine or toluidine blue. They are most likely of a lipoid nature, but in this case their chemical properties could not be studied in detail, as it was not possible to obtain frozen sections.

COMMENT

Definite changes were present in the motor areas of the brain. They were of a degenerative nature and of the same histologic structure as similar foci in the spinal cord. As in the spinal cord, only the white matter was affected, though it was less disintegrated. Thus, fewer gitter cells and fewer myelophages were in evidence than are usually seen in the spinal cord under similar conditions. Instead, a number of cytoplasmic glia cells (cytoplasmic astrocytes) were present. Some authors (Henneberg,[6] and Weil and Davison[7]) believe that the widespread destruction of the spinal cord that results in status spongiosus is a manifestation of deficiency of glia, which, in their opinion, in pernicious anemia is affected by the same toxic substances that destroy the spinal parenchyma. The presence of cytoplasmic glia in some areas in my case denotes, in contrast, a progressive reaction on the part of the glia, which is always present when the nerve parenchyma undergoes degeneration. The large masses of degenerative products cannot be removed in time by the glia, as the breaking up of the nerve fibers is massive and continuous; hence the vast accumulations of the products, which are typical of early nerve degeneration, occur. In the brain such large accumulations of broken-up and degenerative nerve tissues do not occur. For this reason the repair, in the form of glial reaction, is more manifest. The presence of many scattered cytoplasmic glia cells also denotes a glial reaction against destruction of isolated nerve fibers or their small bundles. Such facts, that is, a manifest reaction of the glia, do not sustain the opinion of the authors cited, but prove that the glia behaves as in any other degenerative condition of the nerves.

Study of the changes in the cortex likewise showed the absence of definite relationship between the blood supply and the degenerative foci; in only one focus was a blood vessel present, but it had no structural changes.

The condition of the subarachnoid space and the choroid plexus deserves consideration. Both showed the presence of lipoids. In the subarachnoid space these were enclosed within the gitter cells; in the choroid plexus they appeared as small granules over the tuft cells. In

6. Henneberg, R.: Klin. Wchnschr. **3**:970, 1924.

7. Weil, A., and Davison, C.: Arch. Neurol. & Psychiat. **22**:966, 1929.

both instances the lipoids most likely came from the degenerated foci of the cerebral parenchyma, which discharges its waste into the subarachnoid space and the ventricles (Hassin), provoking in them the reactive phenomena already described.

The structural changes did not correspond with the clinical symptoms, for the patient had no cerebral manifestations. The reason is most likely the scarcity of the changes in the brain, which appeared only as small foci. As has been pointed out, they did not affect the cortex, but were situated in the subcortical area of the motor region. Cerebral manifestations that might have been produced by these minute subcortical foci may have been overshadowed by the signs of degeneration of the spinal cord.

EXTENSIVE GENERALIZED TORULOSIS IN A CHETAH OR HUNTING LEOPARD (CYNAELURUS JUBATUS)

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AND
HERBERT L. RATCLIFFE, M.D.
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Torulosis, an infection caused by Torula histolytica, is known to occur in man throughout the world.[1] Its chief characteristic is the tendency for the yeast cells to localize in the central nervous system, where they produce chronic cystic meningo-encephalitis. The symptoms are mainly those of meningitis and are referable to the lesions in the brain, cord and meninges. Involvement of other organs is uncommon.

The histopathology of torulosis of the central nervous system is peculiar and characteristic. The irregular thickening of the meninges by fibrosis, together with infiltration by mononuclear phagocytes, small giant cells, lymphocytes and plasma cells is not particularly distinctive. However, polymorphonuclear leukocytes are conspicuous by their absence. Highly characteristic, on the other hand, are the large number of yeast cells and the type of focal lesion which they cause. The cells are contained in great numbers within the cytoplasm of the mononuclears and giant cells, but others are free in the tissue spaces. When lesions are present in the brain they may be either cystic or solid, single or multilocular. Singularly, inflammatory reaction is lacking when the cysts occur in the brain substance, but in the meninges there are notable accumulations of mononuclears and infiltrations of perivascular tissues by lymphocytes and plasma cells.

In other organs the histopathologic picture may be essentially the same. At places there is no recognizable tissue reaction against the micro-organisms, while at other places the lesions may consist of areas of granulomatous change in which normal tissues are replaced by colonies of yeast cells surrounded by (usually minor) accumulations of mononuclear and giant cells. Again, a reaction like that of tuberculosis, with its zones of endothelioid cells and lymphocytes, may occur around the parasites, but this is relatively uncommon.

From the Laboratory of Comparative Pathology, Philadelphia Zoological Gardens, and the Laboratory of Dermatological Research, University of Pennsylvania.

1. Stoddard, J. L., and Cutler, E. C.: Monograph Rockefeller Institute no. 6, 1916. Freeman, W.: J. f. Psychol. u. Neurol. **43**:236, 1931.

So far as can be determined from the available literature, only one other case of spontaneous torulosis has been reported in a lower animal; this occurred in a horse, in which the disease was confined to the lungs.[2] The disease has not been reported in the large collection of wild animals maintained by the London Zoological Society,[3] where the beasts are closely examined at necropsy, or from other menageries. Furthermore, generalization such as was observed in this animal occurred in only three of the forty-four cases in man recently collected by Freeman.[4] Indeed, the massiveness of involvement, particularly of the kidneys and spleen, has not been matched in any case thus far reported, either in man or in lower animals.

REPORT OF CASE

History.—The present case, the first instance of torulosis encountered in more than ten thousand consecutive autopsies performed as a routine on wild animals dying in the Philadelphia Zoological Gardens, concerned a male chetah or hunting leopard, Cynaelurus jubatus. This animal, which had been acquired as one of two cubs, had grown with its fellow to maturity while on exhibition in the garden for five and one-half years. Symptoms were not noted until about a month before death, when the animal was reported as "stiff in the hindlegs." One week later he refused all food except milk and appeared to be completely blind. Death occurred five days later.

Necropsy.—At necropsy the body was fairly well nourished. The skin and subcutaneous tissue, as well as the skeleton and musculature, were normal.

The spleen was approximately four times normal size, measuring 38 by 12 by 7 cm. in its greatest dimensions; it was firm and extremely friable. The surface was irregularly elevated by large numbers of closely placed and occasionally confluent, firm, roughly spherical, pale gray nodular masses, several of which were pedunculated. They varied in diameter from 0.1 to 5 cm., and had indistinct outlines which merged with surrounding tissue. On section, the organ was found to be involved throughout its entire extent, the tissue being pale yellow in general, with red-brown and yellowish mottlings. It was firm and friable but free from gross evidence of softening or degeneration. Hemorrhagic areas were numerous on the surface of the section, especially about the larger nodules.

The kidneys were about twice normal size, measuring 10 by 6 by 4 cm. The capsules were irregularly adherent. The external surfaces were largely covered by numbers of small, firm, pale gray, ovoid nodules with indistinct outlines, measuring about 0.5 cm. on cross-section. On the surface of the section similar nodules were found, particularly along the corticomedullary junction, where they sometimes formed continuous, irregular, bulging zones much paler than the surrounding tissue, but apparently of the same consistency.

The retroperitoneal lymph nodes were enlarged, firm and pale gray; the normal architecture was not recognizable grossly.

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2. Frothingham, L.: J. M. Research **3**:31, 1902.

3. Proc. London Zool. Soc., 1900-1932.

4. Fitchett and Weidman have reported a fourth case, with involvement of the kidneys, pancreas, spleen, and lymph nodes, in addition to the cerebrospinal nervous system (Arch. Path. **18**:225, 1934).

Fig. 1.—Hugely enlarged spleen covered by white nodules of torular infiltration.

Fig. 2.—Kidney; this is like the spleen in its huge enlargement and in the presence of white nodules.

The meninges did not appear thickened or adherent when the brain was first removed. Furthermore, there was no evidence of parenchymatous involvement until the brain was examined after fixation. This is also frequently the case in man. After fixation, numbers of small, roughly spherical areas of softening from 0.1 to 0.2 mm. in diameter were found in the cerebral cortex, basal ganglions and pons. As seen on the cut surface of the brain, these areas appeared as sharply outlined individual cysts filled with homogeneous, gray-white, translucent jelly-like substance. The latter was retracted at the center, giving a shallow depression. Inflammatory response was lacking around the lesions.

The spinal cord was not examined.

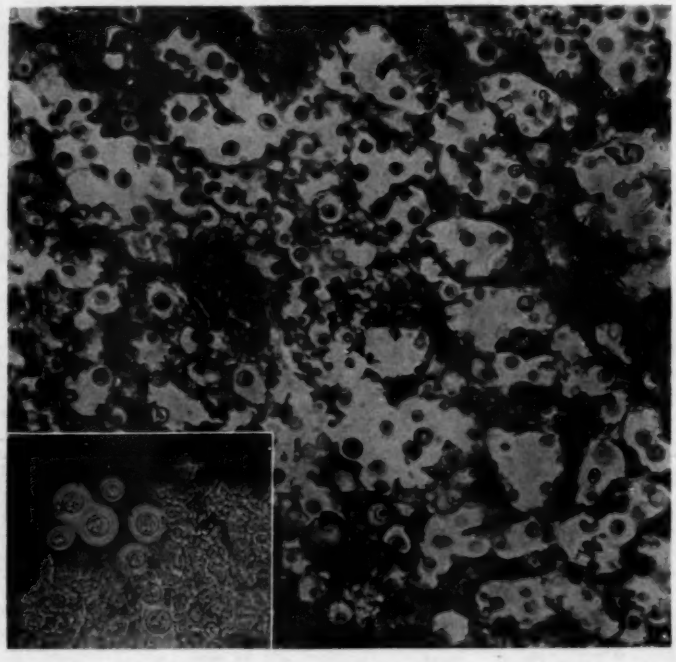

Fig. 3.—Diffuse infiltration of the splenic pulp by yeast cells. The insert shows a group of torula cells scraped from the surface of the spleen, with their characteristic halos (mucinoid envelops); wet india ink preparation.

Microscopic Notes.—Spleen: Except for the capsule, some fragments of trabeculae and an occasional splenic nodule, nothing remained of the normal structures. The tissue was replaced largely by an eosinophilic, hyaline reticulum containing occasional fibroblasts and indistinctly outlined giant cells. Contained in this reticulum were numerous small (from 4 to 10 microns), doubly contoured spherical bodies, which will be described in detail in a later paragraph. They occurred singly or in groups in the reticulum and in the giant cells.

In the interstices of the reticulum were also occasional multinucleated cells, together with macrophages containing the invading organism, not to mention the large numbers of unengulfed organisms. Occasional areas in the trabeculae and capsule had the appearance of recent involvement, as shown by the presence of

a young type of fibrous tissue and small numbers of macrophages. Other than this, inflammatory reaction was entirely lacking.

Kidneys: The parenchyma of both the cortex and the medulla was extensively and irregularly replaced by granulation tissue. Macrophages and small giant cells were numerous throughout the lesions, almost all of which were distended by large and small yeast cells. The nodules on the capsular surface were also made up of such inflammatory growths and infiltrations. Unengulfed yeast cells were rare in the tissue spaces. The most conspicuous of such "free" groups were located within the lumens of glomerular capillaries or in tubules. In the latter situation the surrounding tissues appeared to have undergone lysis, and macro-

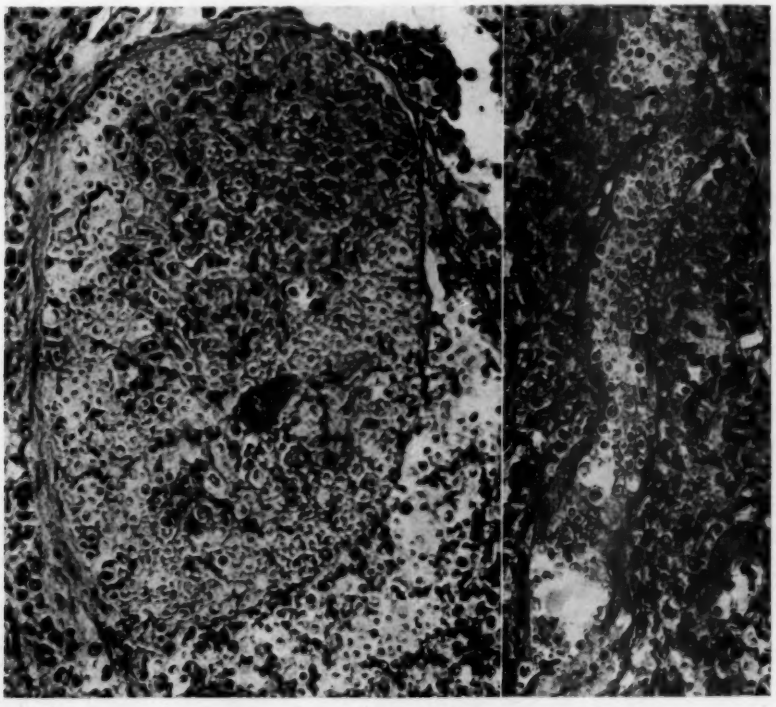

Fig. 4.—Section of the kidney; details of the yeast cells do not show up well, but there are great numbers in both the tuft itself and the subcapsular space; the tubular lumens also contain yeast cells.

phages were absent. Yeast cells were also occasionally observed filling the lumens of small blood vessels. Plasma cells and lymphocytes were present in dense masses, both adjacent to these lesions and apart from them.

Lymph Nodes: The retroperitoneal lymph nodes were practically completely necrotic, except for the capsule and for the occasional persistence of blood vessels. The latter were surrounded by a narrow band of lymphocytes. Yeast cells lying either free or in an eosinophilic coagulum replaced the lymphoid elements.

In the mesenteric lymph nodes the yeast cells were arranged in the form of small colonies. These were located mainly in the cortical nodes which consisted of more or less discrete foci in which the normal lymphoid elements were

replaced by macrophages containing numbers of parasites. The medullary and peripheral sinuses of the lymph nodes were often distended by a similar type of macrophage. Few of these contained yeast cells.

Liver: Sections of this organ contained numerous small (from 50 to 200 microns) sharply outlined rounded areas in which the parenchyma had been replaced by accumulations of macrophages and small giant cells. The yeast cells lay within the cytoplasms of the latter. Occasionally, polymorphonuclear neutrophils and lymphocytes were also present within the smaller lesions. These foci were not related to any special structures of the liver (portal vein, artery or duct).

Suprarenal Glands: Lesions similar in most respects to those of the liver were present in the midzone of the cortex of the suprarenal gland. In larger lesions the inflammatory elements had undergone necrosis in the central parts, leaving the yeast cells free in a turbid basophilic mass.

Lungs: Changes in these organs which may be attributed to torulosis were of minute size and consisted of circular or fusiform thickenings of the alveolar walls or interlobular septums. There was a moderate fibrous tissue overgrowth in these areas, together with accumulations of macrophages (containing parasites) and lymphocytes.

Brain: There was an irregular thickening of the pia-arachnoid, which was most pronounced in the depths of sulci. This was largely referable to hyperplasia of fibrous tissue, edema and cellular infiltrations and was most marked when yeast cells were also present. Many of the latter were contained within the cytoplasm of macrophages, but they also occurred free in tissue spaces. Occasionally, groups of parasites lay in spaces in the thickened meninges. Within the parenchymatous nerve tissue the lesions due to torulosis consisted of single or multilocular cysts. The smaller of these were made up mainly of masses of closely placed mononuclear phagocytes and small giant cells, which had replaced almost all the normal tissue elements. These cells contained large numbers of the parasites, but the latter also occurred occasionally between the cells. No inflammatory response was evident around these lesions, except for conspicuous accumulations of lymphocytes about the blood vessels which passed adjacently to the periphery or into the cysts. In many cysts none of the normal cerebral tissue remained except patent blood vessels—arterioles with dense mantles of lymphocytes and widely distended perivascular lymph spaces. In other cysts, bands of glial tissue, usually associated with blood vessels, divided the lesions. Peripheral compression of tissues about the cysts was inconspicuous. Macrophages containing yeast cells were present in the nerve tissue immediately adjacent to the lesion.

THE INFECTING ORGANISM

Unfortunately, an attempt was not made to cultivate the organism from tissues at necropsy. In fact, infection was not even suspected at that time, since appearances seemed to indicate a neoplasm. However, examination of the sections and wet smears from the various organs allowed identification of the micro-organism within certain limits, particularly since its morphologic appearance and singular tissue changes corresponded so closely with those already well known in man.

In sections, the organism was sometimes perfectly spherical, but usually was distorted. It varied between 4 and 12 microns in diameter. It had a thick, refractile shell surrounded by a relatively thick capsule (this was best seen in the containing one or two large clear vacuoles and a small amount of chromatoid larger cells). In the interior there was a small amount of eosinophilic cytoplasm

substance. As a rule, the cells free in tissue spaces lay in a thin, eosin-staining matrix. In the case of larger cells, one or several small ones frequently occurred in juxtaposition. This was clearly an expression of budding, since all stages, from the first extension of the protoplasm to the formation of the daughter cell (or even cells equal in size to the parent cell), were seen. Reproduction within large cells (asci) was not recognized.

In wet smears from the involved organs, prepared by scraping material from the cut surface and suspending it in saline solution or india ink, the bodies appeared as highly refractile spheres from 4 to 14 microns in diameter. Many showed budding; this was sometimes multiple, and occasionally the buds were arranged in a chain consisting of two or three small daughter cells. In such preparations the thick mucinoid capsule was especially evident, and within it, in turn, the double capsule around the parasite could be seen to advantage.

There can be little doubt that the infecting organism in this case was a yeast, but it is hardly possible to make further and final identification without cultures. Still, the limited number of species involved in torular infection, their tendency to be confined to certain anatomic locations—notably the cerebrospinal system—the uniformity with which T. histolytica is identified in cases of cerebrospinal involvement and the singular type of tissue reaction associated with such infection must permit tentative identification of the parasite in this case as T. histolytica.

ANIMAL TESTS

These tests centered around the question whether Felidae in general were susceptible to infection with T. histolytica. We found that rats are highly susceptible on intrameningeal inoculation, and Freeman's monograph indicates the consistency with which guinea-pigs also can be infected. To our surprise, the cat was found to be highly resistant, even on intrameningeal inoculation. In each animal the brain (and sometimes other organs) was examined histologically.

CAT 1.—This animal was inoculated with strain 664, which had produced frank torular meningitis which killed a rat within seven weeks. The cat died within ten days, without any evidence of successful invasion.

CAT 2.—This animal was inoculated in the same manner as cat 1. It was killed at the end of three months. The meninges were moderately infiltrated with yeast cells.

CAT 3.—Strain 1725, employed here, was the most virulent of twenty strains of T. histolytica with which we had worked. It had induced generalized torulosis in each of four rats tested, involving no less than three, and sometimes five, of the following organs: brain, lungs, liver, spleen and kidney. The cat was killed at the end of one month, but did not disclose any lesions either at necropsy or on histologic examination. T. histolytica was, however, secured from the meninges by retroculture.

CAT 4.—Strain 2249 was one recently cultured from a human patient with a widely generalized infection. When injected into a rat, it involved the brain, pancreas, kidney and spleen. The cat died within four and one-half weeks, without any evidence of torular infection.

CAT 5.—This animal was inoculated with the same strain employed in cat 4. It died within nine days, showing torular infiltration of the cerebral meninges of such a mild grade that it suggested an infection that was dying out.

The consistency with which all five animals were unaffected, even though three different strains (two of which were highly infectious for rats) were

employed, in the face of such a severe test as injections directly into the meninges, stamps the cat as among the genera resistant to torulosis. From this it might be (superficially) deduced, by analogy, that the chetah, a co-feline is similarly resistant to T. histolytica and that a different species of Torula was concerned in it. We do not subscribe to such a conclusion. It is well known that among rodents the guinea-pig is relatively resistant to experimental blastomycosis, whereas the rat is highly susceptible. Indeed, until it is proved otherwise, we believe that the burden of proof lies on those who would discredit T. histolytica as the cause of the morbid anatomic changes which were so distinctive in the chetah and which compared so closely in morphologic features and tissue reactions with torulosis in man.

SUMMARY

A second instance of torular infection in a lower animal is recorded in a chetah which died in captivity. It is only the fourth instance in which the infection was widely generalized, either in man or in lower animals. The spleen and kidneys were massively enlarged, far beyond the size yet recorded for man in those organs. Lesions in the cerebral cortex were cystic, as they frequently are in man. Although the organism was not secured in culture, its morphologic features in lesions and the distinctive tissue changes were so similar to those seen in man that the organism can be identified tentatively, at least, as T. histolytica. Cats were found to be strongly resistant to infection with three different strains of rat-virulent T. histolytica on intrameningeal inoculation.

INFLUENCE OF DRUGS USED IN ANTISYPHILITIC THERAPY ON THE RETICULO-ENDOTHELIAL SYSTEM

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Little is definitely known concerning the manner of the prophylactic or curative action of the drugs used in the treatment of syphilis. Since Ehrlich applied his side-chain theory of immunity to chemotherapy many investigators have advanced different theories as to the mode of action of arsenicals in vivo. There is as yet a lack of complete agreement, but the generally accepted idea is that the action is probably due to a combination of factors rather than to one factor alone. Kolmer [1] suggested that a new substance may be formed by combination between the injected drug and the proteins of the blood or tissue; there may be chemical change by oxidation or reduction, or antibody formation may be stimulated by the injected drugs. The fact that arsenical drugs, such as the arsphenamines, do not exert the same spirocheticidal action in vitro that they do in vivo shows that the action is not a simple chemical one of the drug on the parasite.

Voegtlin and Smith [2] first advanced the hypothesis that arsenical compounds must be changed to one type, namely, the trivalent oxides RAs:0, before exerting their principal toxic action. These substances are formed by oxidation of trivalent and reduction of pentavalent arsenicals, respectively. Subsequent work by Voegtlin and others supported this idea, and Rosenthal [3a] devised a method of demonstrating arsine oxide in vitro and in vivo. He was able to recover from 10 to 12 per cent of injected arsphenamine as arsine oxide from the liver of the rat from three to four hours after injection. A comparable concentration was demonstrated in the rat kidney after the injection of neo-

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This work was aided by funds from the Committee on Research in Syphilis, Incorporated, the Douglas Smith Foundation and the A. B. Kuppenheimer Foundation.

1. Kolmer, J. A.: Principles and Practice of Chemotherapy, with Special Reference to the Specific and General Treatment of Syphilis, Philadelphia, W. B. Saunders Company, 1926.

2. Voegtlin, Carl, and Smith, H. W.: J. Pharmacol. & Exper. Therap. **15:** 475, 1920.

3. Rosenthal, S. M.: (*a*) Pub. Health Rep. **47:**933, 1932; (*b*) ibid. **47:**241, 1932.

arsphenamine. Failure to demonstrate arsine oxide in other organs and tissues was attributed to probable low concentrations.

Some interesting work has been done in an endeavor to explain the mechanism of the oxidation and reduction reactions in vivo. Hopkins and Dixon [4] showed that glutathione is concerned in biologic oxidation and reduction. Hopkins [5] isolated from mammalian muscle a tripeptide containing cysteine and showed that the sulphydryl group in that molecule can undergo reversible oxidation-reduction. Voegtlin, Dyer and Leonard [6] explained the toxicity of the arsine oxides by the hypothesis that they are specific poisons for the sulphydryl group in glutathione and possible other sulphydryl compounds which may occur in protoplasm. Rosenthal [3b] demonstrated the ability of sulphydryl groups to combine with arsenoxide, but not with pentavalent arsenic. He also showed that trivalent arsenic does not combine with native proteins containing no sulphydryl groups.

Aschoff [7] revived interest in fixed phagocytic cells of the body by grouping them together under the name of the reticulo-endothelial system. This includes the phagocytic cells of the spleen, liver, bone marrow and lymph nodes and the histiocytes of the connective tissue. This system can be readily studied because the cells phagocytose and retain for varying periods such substances as lithium carmine, trypan blue, india ink, saccharated iron oxide and colloidal metallic compounds, e. g., of silver, mercury, bismuth and copper. When the reticulo-endothelial system has taken up large quantities of these substances it is said to be "blocked," with reduction of certain functions. It has been shown, however, that complete dysfunction does not obtain. Various functions have been assigned to this system of cells, including, in addition to their phagocytic properties, participation in antibody formation and alteration of chemical substances injected for therapeutic purposes. Several observations have been made relative to drugs used in syphilotherapy. Del Baere [8] showed that neoarsphenamine remains longer in the circulation after an injection of solution of pituitary and also that after an injection of neoarsphenamine substances such as congo red and emulsified fat, which are known to leave the blood stream by way of the reticulo-endothelial system, remain longer in the circulation. This is supportive evidence of Schlossberger's [9] idea that neoarsphenamine leaves the blood stream, at least in part, by way of the reticulo-endothelial system. This is probably due to the fact that it is a semi-

4. Hopkins, F. G., and Dixon, M.: J. Biol. Chem. **54**:527, 1922.

5. Hopkins, F. G.: Biochem. J. **15**:286, 1921.

6. Voegtlin, Dyer and Leonard: Pub. Health Rep. **47**:1882, 1932.

7. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924.

8. Del Baere, L. J.: Wien. klin. Wchnschr. **38**:1131, 1925.

9. Schlossberger, H.: Centralbl. f. Bakt. (Abt. 1) **110**:210, 1928.

colloid. The therapeutic action of arsphenamine has been shown to be absent in mice and rabbits which have been infected with the organism of relapsing fever and which have been splenectomized and "blocked" with saccharated iron. When this work was repeated in animals infected with Spirochaeta pallida and Trypanosoma equiperdum the results were otherwise. Schamberg, Kolmer, Rule and Madden [10] came to the following conclusions:

1. Partial "blockade" of the cells of the reticulo-endothelial system of rats by intravenous injections of India ink slightly increased resistance to infection with Tryp. equiperdum.

2. This partial "blockade," however, had no demonstrable effects upon the trypanocidal activity of arsphenamine and neoarsphenamine.

3. Partial "blockade" of rabbits by intravenous injections of India ink had no appreciable effects upon infection with Spirochaeta pallida.

4. This partial "blockade" of rabbits likewise had no demonstrable effect upon the spirocheticidal properties of arsphenamine and neoarsphenamine.

5. Removal of the spleens of rats had no appreciable effects upon the development and course of infection with Tryp. equiperdum inoculated intraperitoneally five to seven days later.

6. Splenectomy, however, definitely reduced the trypanocidal activity of both neoarsphenamine and arsphenamine given five to seven days later, since the minimal curative doses were almost twice as much as observed among control animals.

7. Removal of the spleens of rabbits had no appreciable influence upon the development and course of acute testicular syphilis of rabbits following inoculation with Spirochaeta pallida approximately three to four weeks after operation.

8. Splenectomy, however, definitely increased rather than decreased the spirocheticidal activity of arsphenamine.

9. While partial "blockade" of the reticulo-endothelial system with India ink had no appreciable effects upon the trypanocidal and spirocheticidal activity of arsphenamine and neoarsphenamine, it is apparent that splenectomy profoundly influences the chemotherapeutic activity of these compounds.

Golowitzina [11] concluded that the reticulo-endothelial system does not constitute the cell complex on which oxidation or reduction in the organism depends.

Goldzieher and Peck [12] blocked white rats with trypan blue, injected mercuric chloride or sulpharsphenamine, killed the animals at various times thereafter and examined the liver and spleen. They found an increase in the number and size of the Kupffer cells of the liver and a noticeable enlargement and vacuolation of the nuclei in the animals treated with mercuric chloride. The enlargement of the cells decreased after a twenty-four hour period, but the nuclear changes persisted. After forty-eight hours there was no demonstrable difference in the

10. Schamberg, J. F.; Kolmer, J. A.; Rule, A., and Madden, B.: Am. J. Syph. **17**:176, 1933.

11. Golowitzina, K. A.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **71**:541, 1931.

12. Goldzieher, M. A., and Peck, S. M.: Arch. Path. **3**:635, 1927.

microscopic picture between the dyed and the undyed animals. In the rats given injections of sulpharsphenamine there was an enormous swelling of the Kupffer cells two hours after the last injection. The nuclear changes were the same as in the animals treated with mercuric chloride. These authors concluded that there was direct stimulation of these cells by the drugs administered.

Von Jancsó [13] suggested the use of the arsphenamines as vital stains for the reticulo-endothelial system, since they are taken up by these cells and may be demonstrated by a silver method. Arsphenamine, silver arsphenamine and neosilver arsphenamine could be found in the reticulo-endothelial system as long as three weeks after injection, and small emboli in capillaries also gave the reaction. After subcutaneous injection the reaction was positive in histiocytes of the skin and subcutaneous tissue. Neoarsphenamine and sulpharsphenamine were found especially in the connective tissue of abdominal organs and only to a slight extent in reticulo-endothelial cells.

EXPERIMENTS

Several series of white rats of approximately the same age and weight were used. Preliminary results were irregular in stock rats, especially in regard to size and vacuolation of the reticulo-endothelial cells. This irregularity of results was also found in control animals. It was thought to be due to previous or present infection, so the work was repeated, using nondiseased rats of the strain obtained from the Wistar Institute. Twenty rats comprised a series; ten were dyed and ten undyed. The dyeing was done by repeated subcutaneous injections of trypan blue.

Five of each group, dyed and undyed, were treated, and the other five were kept as controls. The following drugs were administered intravenously: neoarsphenamine, thio-arsene (disodium salt of bismuth [p-sulphophenyl] [p-acetamidophenyl] dithio-arsenite), colloidal bismuth, mercurosal, tryparsamide and gold sodium thiosulphate. The following drugs were administered intramuscularly: sulpharsphenamine, bismuth arsphenamine sulphonate, potassium bismuth tartrate, mercuric chloride and sodium cacodylate. The doses were about seven times the therapeutic doses in man, which are comparable to those used by Goldzieher and Peck.[12] The intramuscular injections were given three times at five day intervals, and the intravenous injections three times at weekly intervals. The animals were killed by bleeding under ether narcosis at intervals of one, three, six, twenty-four and forty-eight hours after the last injection, and the liver and spleen were examined.

Frozen sections were studied by the following methods:

1. Silver method of von Jancsó. Tissue is fixed from one to four days in solution of formaldehyde, and frozen sections are made. To a 1.5 per cent aqueous solution of silver nitrate as many drops of ammonium hydroxide are added as are necessary to make the solution again clear. An equal amount of double distilled purest glycerin is added. Sections are placed in this solution for from thirty to thirty-five minutes. The arsphenamine derivative stains brown or black. The sections are washed in distilled water for one minute and placed in 1 per cent aqueous sodium thiosulphate solution for from three to ten minutes.

13. von Jancsó, N. Jr.: Ztschr. f. d. ges. exper. Med. **61**:63, 1928.

They are then dehydrated and mounted in balsam. They may be counterstained if desired. This method depends on the reduction of ammoniacal silver nitrate by arsphenamine in the tissues. As is the case with all silver methods, results were irregular in various sections and even in different parts of the same section in our study. Positive results were found only with the arsphenamines. In the case of thio-arsene, which is a good spirocheticidal drug somewhat different chemically from arsphenamine, no change of any kind was seen in the tissues. Positive results were manifested by the appearance of granules in macrophages (fig. 1) and browning of some of the connective tissue structures as well as, occasionally, the nuclei.

2. Nitroprusside reaction. To determine whether sulphydryl compounds were present in appreciable amount in the macrophages of the liver and spleen and

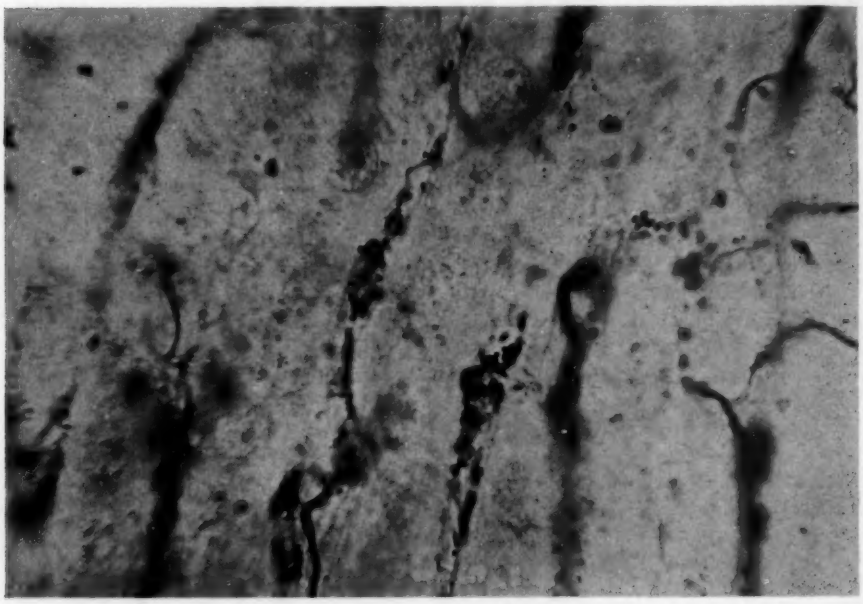

Fig. 1.—Liver of rat which had received neoarsphenamine intravenously; the Kupffer cells contain dark brown granules; von Jancsó silver method.

might take part in the oxidation-reduction reactions, they were examined by the following method:[14] Frozen sections about 40 microns thick are floated onto microscopic slides with as little soaking in water as possible. They are then treated successively with 10 per cent zinc chloride, 5 per cent sodium nitroprusside in 15 per cent ammonium sulphate and 2 per cent ammonia. The reagents are added from a dropping pipet, and each is added about thirty seconds after the preceding one. It is desirable to pour off each reagent, without washing, before the next is added. A positive reaction consists of a pinkish coloration in tissues containing large amounts of sulphydryl derivatives. In the animals studied the reaction was negative, which shows that the substances were not present in sufficient quantity to give a positive reaction, such as can be obtained in sections of epidermis.

14. Percival, G. H., and Stewart, C. P.: Brit. J. Dermat. **42**:215, 1930.

Paraffin sections were studied by the following methods:

1. Delafield's hematoxylin stain, as used by Goldzieher and Peck.[12] By this method the general morphology of the tissue could be studied. With stock rats certain changes were noted, namely, enlargement of macrophages, with occasional phagocytosis of red cells. These findings were not uniform and were also seen in controls. When the work was repeated, using an infection-free strain of rats obtained from the Wistar Institute, no appreciable changes in the macrophages could be seen, except enlargement in the case of the animals in which a dye had been injected. Certain granules were seen in the macrophages, and the following method was used for their study.

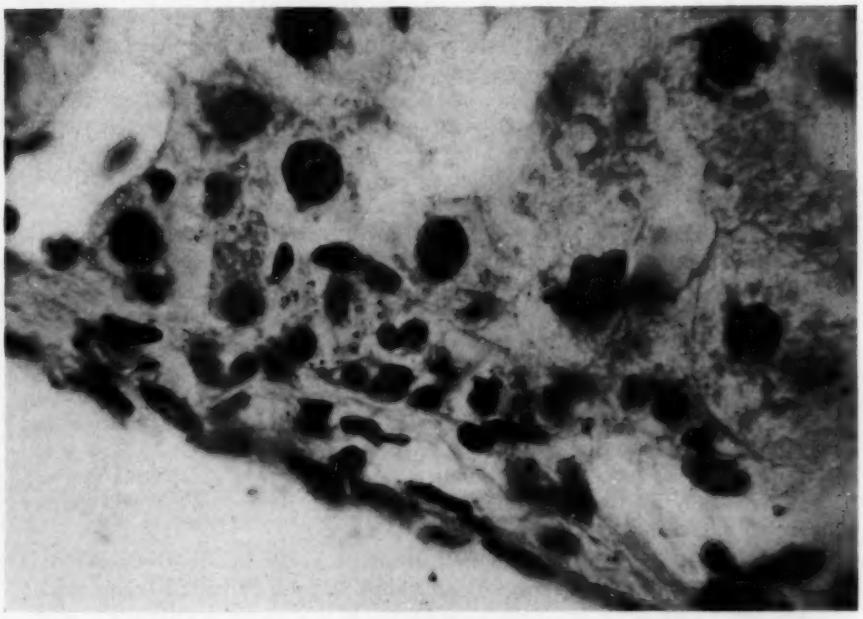

Fig. 2.—Liver of rat which had received neoarsphenamine; brownish granules are seen in macrophages about the central vein of the lobule; Delafield's hematoxylin stain.

2. Pyronine methyl green. This method stained alcohol-fixed tissue sufficiently for orientation without masking cell inclusions. It also furnished a contrast stain to the yellowish-brown granules which were found in the animals studied after the administration of certain drugs. Following the injection of bismarsen, potassium bismuth tartrate, sodium cacodylate and tryparsamide, no granules were seen in the macrophages. Following the injection of neoarsphenamine, brownish granules were seen in Kupffer cells about the central vein of the lobule (fig. 2) one, three and six hours after death and about the large vessels in the spleen three hours after death. Following the injection of sulpharsphenamine, granules were found in the spleen one and six hours after death and in the liver three and six hours after death. After the injection of colloidal bismuth, brown granules were found concentrated in the intermediate zone in all sections of liver and in the spleen

six, twenty-four and forty-eight hours after death. Following the administration of mercuric chloride, brownish granules were found in the liver and spleen six and twenty-four hours after the last treatment. After the injection of gold sodium thiosulphate, granules were found in the liver of the animals examined three and six hours after death and in the spleen of those examined six hours after death. All granules did not give the iron reaction. Similar granules were found in the liver of a patient who died with arsphenamine dermatitis. Professor Pautrier of the University of Strasbourg kindly permitted us to study sections from this patient.

3. Hydrogen sulphide method of Justus, as modified by Brünauer and later by Osborne.[15] The sections prepared by this method did not differ from the control sections, except that they contained some of the brownish granules already mentioned. All sections, including the controls, contained the greenish crystals described by all workers, which were assumed by them to be arsenic trisulphide. Further study of this method by Tannenholz and Muir[16] showed that the visible bodies were crystals. They were not soluble in sodium hydroxide, which will dissolve arsenic trisulphide. Treatment of egg albumin alone and of egg albumin containing sodium arsenite, red blood cells and blood serum, respectively, with hydrogen sulphide produced the same crystals; these were present in greater numbers in the material containing blood serum. An exsanguinated heart showed the crystals only in the muscle cells, while in a heart containing blood they were present throughout. Treatment of the tissue with hydrogen sulphide in an acid medium before fixation did not produce the crystals. Alcoholic fixation before treatment with hydrogen sulphide also was not followed by production of the crystals. It was concluded that the crystals may be a sulphur-protein compound and that they have not yet been proved to be crystals of arsenic trisulphide. In an effort to demonstrate arsenic in tissues, Tannenholz and Muir treated sections with silver nitrate, but could find no difference between those containing arsenic and the controls. The colorimetric method for demonstrating arsenic and phosphorus, which was introduced by Denigès and later modified by Truog and Meyer, was found unsatisfactory, because of large amounts of phosphorus and iron.

It is probably correct to say that at present there is no method that will identify arsenic in microscopic sections.

4. Iron reaction. Kyes utilized the berlin blue reaction to study macrophages in pigeons. This method was found to be not applicable to human beings, owing to the small amount of hemosiderin contained in the macrophages.

COMMENT

When nondiseased rats were used, the marked changes in the cells of the reticulo-endothelial system reported by Goldzieher and Peck were not seen, although similar changes were seen irregularly in stock rats. By means of the silver impregnation method of von Jancsó, granules might be seen in the macrophages in some sections, and in sections stained by pyronine methyl green brownish granules might be seen in macrophages in various portions of the lobules of the liver. There is no doubt that the reticulo-endothelial cells participate in the handling of various antisyphilitic drugs, but whether they take them up as they

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would many other substances injected intravenously, owing merely to their phagocytosing properties, or whether they have an important part in chemotherapeutic processes, cannot be said on the basis of the evidence at hand. The ability of arsine oxide to combine with sulphydryl compounds suggests that the macrophages may be rich in these substances. The nitroprusside reaction was not positive, showing that these cells do not contain so high a concentration as does the epidermis, in which the reaction is positive. The finding of similar, although slightly different, granules in different portions of the lobules of the liver and at varying times after the injection of various drugs suggests that the liver handles each one in a different manner. The exact nature of the granules was not determined. They did not give the iron reaction, so they were not hemosiderin. They may have been a proteinate of the metal injected. The evidence at hand neither proves nor disproves the participation of the reticulo-endothelial cells in chemotherapeutic processes. Considerable study was made of the hydrogen sulphide method for demonstrating arsenic in tissues, and it was impossible to prove that the crystals demonstrated were arsenic trisulphide. They may have been a sulphur-protein compound.

SUMMARY AND CONCLUSIONS

Nondiseased white rats were given the following drugs intravenously or intramuscularly: neoarsphenamine, thio-arsene, colloidal bismuth, mercurosal, tryparsamide, gold sodium thiosulphate, sulpharsphenamine, bismuth arsphenamine sulphonate, potassium bismuth tartrate, mercuric chloride and sodium cacodylate. The dosages corresponded to about seven times the recognized therapeutic dose for adults. Half of the animals were given trypan blue, and half were left undyed. After the injection of neoarsphenamine, sulpharsphenamine, colloidal bismuth, mercuric chloride, gold sodium thiosulphate and thio-arsene, brownish granules were seen in macrophages in various parts of the lobules of the liver in sections stained with pyronine methyl green. After silver impregnation, granules were found irregularly after the injection of neoarsphenamine. No significant morphologic change was seen in the macrophages following the injection of the aforementioned drugs. No difference was observed between "blocked" and "unblocked" animals. This study shows that the reticulo-endothelial system undoubtedly participates in disposing of many drugs injected intravenously, but its actual function in chemotherapy is not definitely known. The reticulo-endothelial cells do not contain sufficient sulphydryl compound to give a positive nitroprusside reaction, so that nothing definite can be said relative to their participation in the oxidation-reduction reaction attributed to those substances. Crystals found in tissues treated by the hydrogen sulphide method for demonstrating arsenic could not be proved to be arsenic.

Laboratory Methods and Technical Notes

A NEW ELASTIC TISSUE STAIN

RAPID METHOD FOR ELASTIC TISSUE, CONNECTIVE TISSUE, FIBRIN AND AMYLOID, EMPLOYING CONGO RED

ARAM A. KRAJIAN, LOS ANGELES

As the significance of pathologic changes involving elastic tissue is increasingly evident, the use of a rapid and specific stain becomes essential. A technic is presented here which demonstrates elastic and connective tissue, fibrin and amyloid. The method depends on the use of congo red, which specifically stains elastic fibers bright red. In addition a slight modification of the procedure is offered for the preparation of permanent sections showing amyloid in a characteristic color.

TECHNIC OF METHOD FOR ELASTIC TISSUE, CONNECTIVE TISSUE AND FIBRIN

1. Fix tissues in 10 per cent formaldehyde twenty-four hours or longer.
2. Cut frozen sections about 10 microns thick.
3. Wash thoroughly in tap water.
4. Place sections in the following stain for ten minutes: 4 per cent aqueous congo red solution (in 5 per cent sodium citrate), 8 cc., and glycerin (chemically pure), 2 cc.
5. Wash quickly in tap water.
6. Transfer sections to 1 per cent aqueous potassium iodide solution for ten seconds (rotating section in the solution).
7. Wash thoroughly in tap water.
8. Place sections in the following stain for from five to ten minutes:

Resorcinol	3.0 Gm.
Aniline blue	1.5 Gm.
Orange G	2.5 Gm.
Phosphomolybdic acid	1.0 Gm.
Distilled water	100 Cc.

9. Wash thoroughly in tap water in a large basin. Float sections onto slides and blot with filter paper very thoroughly.
10. Dehydrate in absolute alcohol for two minutes, changing alcohol twice (dropping bottle method).
11. Clear in pure xylene.
12. Mount in gum damar.

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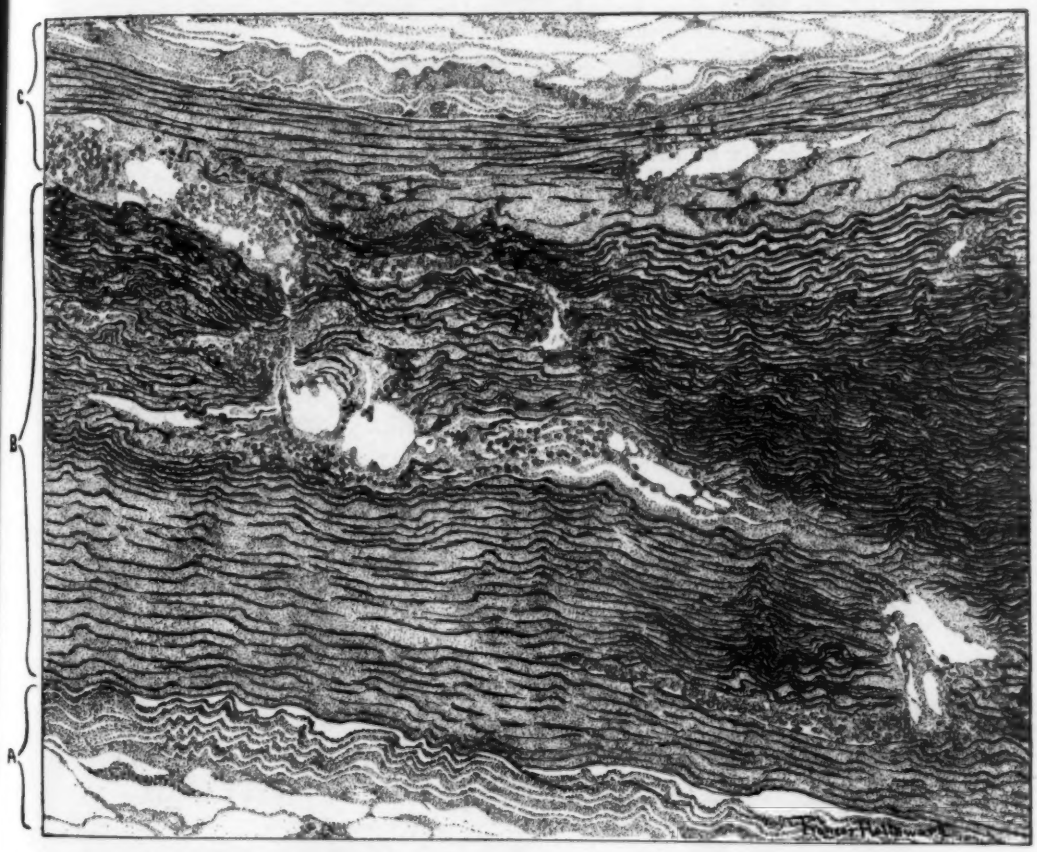
This method gives a colorful, well differentiated preparation that keeps well when protected from direct exposure to light.

Elastic fibers appear bright red; fibrin and connective tissue, dark blue. Red blood cells are colored orange yellow.

Sections embedded in paraffin may be used satisfactorily, but require longer staining periods. The staining technic is the same as for frozen



Elastic tissue stained with congo red. A section of aorta shows syphilitic mesa-ortitis with disintegration of elastic plates. The red-stained elastic fibers in the section are seen as deep black in the drawing. *A* indicates the fibrous connective tissue of the adventitia; *B*, media, showing extensive destruction of the elastic fibers by areas of necrosis and cellular infiltration, and *C*, the intima, thickened by atherosclerotic changes.

sections except that it requires thirty minutes staining in the congo red solution and thirty minutes in the aniline blue solution.

If nuclear staining is desired in addition to differentiation of elastic tissue, use the technic for staining amyloid given herewith.

MODIFIED TECHNIC FOR STAINING AMYLOID

1. Stain loose frozen sections in Harris' hematoxylin about fifteen seconds and wash thoroughly in tap water until sections are light blue.

2. Transfer sections to 4 per cent aqueous congo red solution with glycerin for fifteen minutes and wash in tap water.

3. Differentiate in 1 per cent aqueous potassium idoide solution and wash thoroughly in tap water.

4. Float sections onto slides and blot with filter paper.

5. Dehydrate in absolute alcohol for two minutes, changing alcohol at least twice.

6. Clear in xylene for from two to five minutes.

7. Mount in gum damar.

Amyloid is stained red and is beautifully differentiated from the surrounding tissues. The clearing of the tissue does not in any way interfere with the amyloid stain and the picture is further enhanced by the hematoxylin nuclear stain. The elastic fibers, also, are stained red, but are of a darker hue and may be easily differentiated from the amyloid.

General Review

EXPERIMENTAL CIRRHOSIS IN RELATION TO HUMAN CIRRHOSIS

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CRITERIA

Medical literature abounds in reports on experimental cirrhosis. Probably no other pathologic condition has been produced by so many diverse methods. Before attempting to evaluate the bearing which these have on cirrhosis in man, it is necessary to consider the essential characteristics of human cirrhosis.

The conception that "cirrhosis" is synonymous with "chronic diffuse hepatitis" is generally accepted. Any agent or combination of agents which produces chronic diffuse hepatic inflammation will result in some degree of cirrhosis. The degree and character of this may vary but the essential features of the cirrhotic process are (1) degeneration and destruction of liver cells, (2) regeneration of liver cells from those which escaped destruction and (3) proliferation of connective tissue.

Portal cirrhosis [1] in advanced stages is accompanied by marked disturbances of the portal circulation. Kretz showed that normally the hepatic and portal veins divide in an arborescent fashion, and the smaller twigs are given off almost at right angles. The two venous systems may be compared to two huge venous trees the branches of which interlace regularly from opposite directions. They end in fine dendritic

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Prepared by assignment for the Second International Conference for Geographic Pathology, Utrecht, July 26-29, 1934.

1. Nomenclature: The term *"portal cirrhosis"* is recommended as synonymous with *"Laënnec's cirrhosis."* This avoids ambiguities implied in other terms and suggests the obstruction to portal circulation which is a regular feature in advanced stages of the disease. The term *"atrophic cirrhosis"* is objectionable because: 1. It implies atrophy, which is not regularly present; frequently the liver is larger than normal. 2. The term is used by some to indicate especially that form which develops following acute yellow atrophy. The term *"alcoholic cirrhosis"* suggests an etiologic agent whose rôle has not been demonstrated. The terms *"monolobular," "perilobular"* and *"multilobular"* are ambiguous since they are not used in the same sense by all writers. The terms *"nodular," "granular"* and *"hobnail"* cirrhosis describe a gross characteristic which may be present in conditions other than *portal cirrhosis.* The term *"Laennec's cirrhosis"* is not objectionable. It has historic significance and is seldom misunderstood.

branches which dovetail alternately. The relationship of the two venous systems is clarified by considering the hepatic lobules in longitudinal sections instead of the cross-sections in which they are usually represented. This histologic aspect is shown diagrammatically in figure 1*A*. Such a

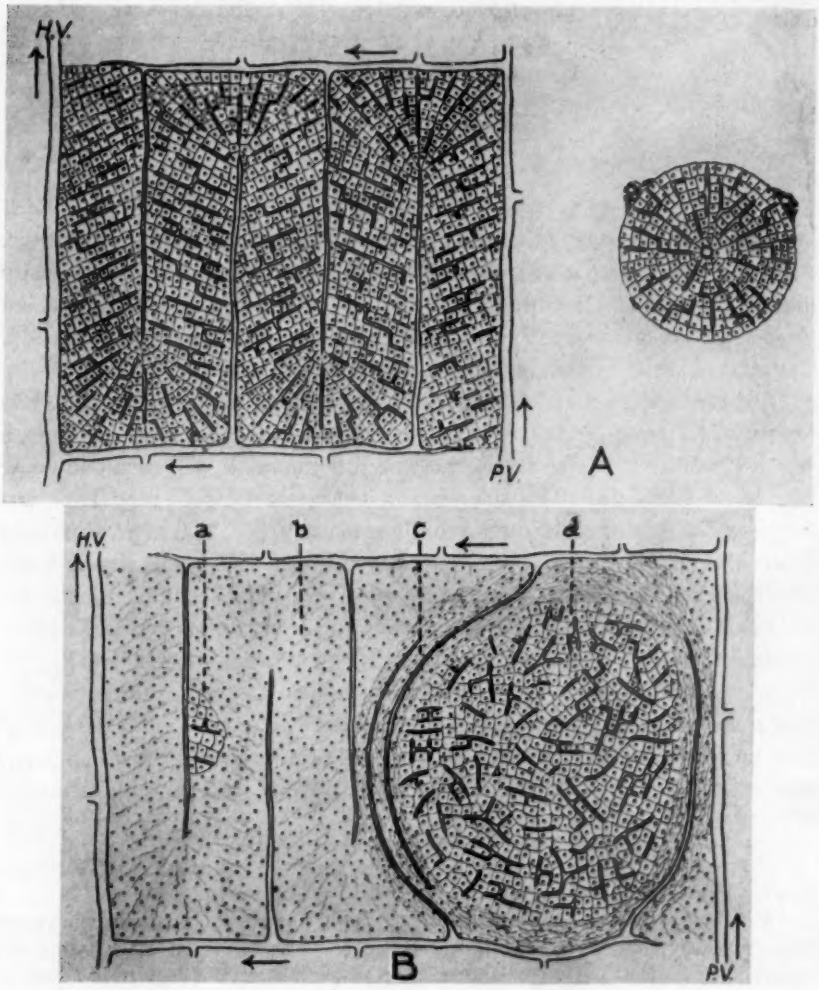

Fig. 1.—*A*, diagram of liver lobules in longitudinal section. This illustrates the alternating arrangement of the hepatic and portal venules more clearly than the conventional cross-section of a lobule. *P.V.* indicates the portal vein; *H.V.*, the hepatic vein.

B, diagram of liver lobules in longitudinal section, illustrating the development of cirrhosis: *b* represents an area of hepatic necrosis, and *a*, a group of intact hepatic cells, which by regeneration would produce an expanding nodule of cells, as *d*, and would compress the collapsed stroma and vessels about its periphery, *c*.

view of the circulation of the normal liver aids in visualizing the histogenesis of portal cirrhosis and its associated circulatory disturbances.

Alteration or destruction of architectural pattern has been noted as a prominent feature of portal cirrhosis by many who have studied this condition closely. Kertz believed that Laënnec's cirrhosis is the result of attacks of degeneration and destruction of liver cells, that the entire parenchyma has been totally renewed several times, and that this results in a complete architectural transformation of the parenchyma. He found that the circulatory relations were markedly disturbed; that an injection mass introduced through the portal vein found its way directly into the hepatic vein leaving much of the parenchyma unpenetrated, and that there were many turgescent nodules of hepatic cells entirely devoid of hepatic veins. These nodules could be reached by injection through the hepatic artery but were largely impervious to injection via the portal vein.

Kelly believed that some injury caused destruction involving areas of liver tissue. As the substance of necrotic cells was absorbed the stroma of those areas collapsed. The expanding force of adjacent regenerating nodules of cells compressed this stroma and the vascular channels contained in it. He emphasized that the chief characteristic of Laënnec's cirrhosis is complete disarrangement of hepatic architecture. The regenerated nodules did not contain radicles of the hepatic vein. Both central and portal veins were diminished in number and were located at the periphery of the nodules. These interpretations and conclusions were later confirmed by McIndoe.

MacCallum gave a concise description of the cirrhotic process:

> The liver-cells are killed in patches—whole lobules and groups of lobules at a time, or only parts of lobules. There remain irregular masses of liver tissue partly disconnected from their bile ducts. . . . The masses of liver-cells quickly increase in size by multiplication of their cells, new capillaries are formed in every direction, and this labyrinth of cells expands, pressing the stroma away on all sides. For a time the liver-cells are normal, but then comes another injury, and many of the hyperplastic nodules are partly destroyed. The whole process is repeated, and not only once, but many times. . . . It is clear that this must lead to an extraordinary distortion of the liver's structure. There are no longer lobules, but only nodules produced by the hyperplasia of smaller groups of cells which were left intact.

McNee expressed the same interpretation in very similar terms. Ghon's description of the essential histologic characteristics of cirrhosis presents the same view. He emphasized architectural alteration with complete disarrangement of the circulation as a prominent feature of Laënnec's cirrhosis. Mann maintained that alteration of architectural pattern is the distinguishing characteristic of Laënnec's cirrhosis. Moon's observations on active cirrhosis led to identical conclusions. In portal

cirrhosis the structural rearrangement is so marked that many observers have compared the nodules to adenomas. Laënnec himself regarded the nodules of regenerated hepatic cells as neoplastic. Figure 1*B* represents diagrammatically the development of this type of cirrhosis.

McIndoe's injection studies of cirrhotic livers showed a marked diminution in the total vascular bed. The main trunks were attenuated and irregularly stenosed. The larger branches were given off at unusually abrupt angles and showed irregular deviations to one side as if displaced by some invisible force. The expansive force of a growing mass of hepatic cells would produce such an effect. It was difficult to find any normal central veins whatever. The disarrangement of the terminals of the portal and hepatic veins was conspicuous. These terminals lay in distorted positions in the stroma surrounding the regenerated hepatic nodules. These nodules had no channels into which an injection could penetrate from the portal vein. He found that such nodules received blood principally through branches of the hepatic artery, the terminals of which are less easily obstructed than those of the portal vein. Thus in advanced cirrhosis a definite portohepatic venous obstruction develops, and the portal blood supply to the remaining parenchyma of the liver is reduced to a minimum, if it is not altogether absent. The principal cause for this circulatory block is the contraction of scar tissue about the terminal twigs of both the portal and the hepatic veins. This mechanism of obstruction explains the portal passive congestion and the ascites which are characteristic of late stages of cirrhosis.

Mann found that the capacity for regeneration is largely dependent on adequate portal circulation. When the portal blood is shunted into the vena cava by an Eck fistula, the regenerative capacity of the liver is markedly reduced. Absence of regeneration was noted following injuries to the liver in dogs with Eck's fistula. Similar injuries in normal dogs were followed by complete restoration. This indicates that in advanced cirrhosis obstruction to the portal circulation hinders regeneration and restoration of the hepatic parenchyma. Furthermore, the progressive increase of fibrous tissue which accompanies the cirrhotic process forms a rigid cage about the remaining parenchyma and by contraction this fibrous tissue limits mechanically the space which the hepatic cells may occupy. In areas adjacent to the capsule this limitation is less effective, and nodules of proliferating cells expand and bulge above the surface, producing the characteristic nodular surface. Interference with the portal circulation and the contracting cage of fibrous tissue hinder effective regeneration of hepatic cells.

Single injuries, or those which act on limited portions of lobules, produce a pathologic picture structurally different from that described.

This picture varies depending on the amount and location of the destruction and of the fibrous tissue proliferation. Occasionally a liver is found showing evidence of varying degrees of chronic diffuse hepatitis but without obliteration of lobules and without evidence of extensive progressive injury. Such cases give none of the clinical manifestations of portal cirrhosis, and the diagnosis of chronic hepatitis, or cirrhosis, usually results from postmortem evidence. Some inflammation and irregular fibrosis may develop wherever destruction of cells occurs. Occasionally the inflammation results in obstruction of bile ducts, producing the features of biliary cirrhosis. In other cases the inflammatory process involves portions of lobules irregularly and even surrounds single cells or small groups of cells. But the lobular pattern in such cases is still recognizable. These variations of chronic hepatitis do not fall readily into any proposed system of classification. The frequency of such cases is exemplified in a series of 10,016 autopsies reported by Mallory. In 590 cases of well marked cirrhosis he found 110, or 18.5 per cent, such atypical cases which he could not classify. Those who have studied chronic hepatitis extensively are less vigorous in their support of exact classification.

Numerous experiments have shown that the liver has a marvelous capacity for regeneration. When large portions of the liver are removed surgically no demonstrable deficiency of hepatic function results. Subsequent examination shows that the liver has regenerated to approximately its former volume. Such regeneration is accomplished by the formation of new lobules of normal size, structure and circulatory supply. The architectural pattern in such regenerated liver is not altered and is indistinguishable from that of the normal liver. When a single severe injury to liver parenchyma is produced by one of the known hepatic poisons, the injured areas often will be restored without fibrosis and without alteration of architectural pattern. The injury may have destroyed three fourths of the cells in each lobule, as shown by biopsy following the injury. Yet shortly they are replaced by multiplication of adjacent cells in the lobules. The architectural pattern is not affected, and fibrosis or other visible histologic changes may not have occurred. This type of result following a single chemical or toxic injury must not be expected to follow continued or repeated injury of similar nature.

In the process of repair following injury, all hepatic structures seem stimulated to proliferation. Not only do cells of the liver regenerate but there is also proliferation of bile ducts, of young fibrous tissue and of Kupffer cells and vascular structures. The numerous experiments in which cirrhosis has been produced experimentally have shown this fact conclusively. Hence proliferation of bile ducts is not a suitable differential criterion.

To recapitulate: The cirrhotic process consists of degeneration and destruction of hepatic cells, followed by regeneration and by fibrous tissue proliferation. It is essentially nothing else than chronic, progressive, diffuse hepatitis. If such destruction is limited in extent, involving only portions of the lobules, no marked structural or functional disturbance results. Biliary obstruction may occur, but there is no obstruction to the portal circulation or obliteration of hepatic architecture.

Varying degrees of minor injury without distortion of pattern lead to varying degrees of chronic hepatitis not easily classified. If accurate histologic classification of these were possible, it would serve no useful purpose.

If there is progressive or repeated destruction affecting extensive areas, the resulting regeneration of hepatic cells produces nodules of parenchyma with abnormal circulatory relations. The radicles of both the portal and the hepatic veins lie on the periphery of the nodule, and are embedded in stroma and proliferated fibrous tissue which, as it contracts, produces obstruction of the portal venules. In such a liver the normal lobular pattern is obliterated. The architecture is altered. There are no longer lobules but only nodules of cells divorced more or less completely from normal circulatory relations.

Many authors have emphasized *destruction of architectural pattern* as a feature of portal cirrhosis, but none have proposed to use it as a differential criterion. It will be so used in the following sections when some criterion is necessary to determine how closely experimental cirrhosis has approximated portal cirrhosis in man.

Caution Required in Evaluating Experimental Cirrhosis in Rabbits.—Many of the experiments on cirrhosis have been made on rabbits. These experiments are difficult to evaluate because rabbits frequently acquire chronic hepatitis with cirrhotic changes. Van Heukelom, von Kahlden, Klopstock, Fischler, Findlay and others have made such observations. Ophüls examined 50 rabbits collected from different sources; he found only 6 with livers that were not diseased. Coccidiosis with varying degrees of chronic hepatitis was found in the majority. Cirrhotic processes were found in some livers in which no coccidiosis could be demonstrated. In Ophüls' opinion, this throws grave doubt on many reports of an experimental production of cirrhosis. He regarded rabbits as entirely unsuitable for such experiments.

Smetana published a detailed study of the life cycle of Eimeria, the parasite causing coccidiosis, of its epidemiology and occurrence and of the various lesions and manifestations of coccidiosis. This disease is almost universal among rabbits, and produces varying degrees of chronic hepatitis. Sometimes an apparently normal liver is found following

mild infection, but often the healing process produces diffuse perilobular fibrosis. This may be accompanied by the formation of pseudolobules producing a picture indistinguishable from true cirrhosis. Smetana stated that it is practically impossible to exclude coccidiosis as the cause when a cirrhotic liver is found in a rabbit. Because of the prevalence of this disease, he urged that rabbits should not be used for experiments on cirrhosis.

These observations make necessary an attitude of extreme conservatism toward all reports of the production of cirrhosis in rabbits.

AGENTS USED IN THE PRODUCTION OF CIRRHOSIS

Numerous agents have been used with more or less success in the production of cirrhosis. These may be grouped as inorganic chemicals, organic substances, serologic agents and infections. In many instances combinations of agents were found more effective than one of the agents alone.

INORGANIC POISONS

Phosphorus.—Numerous reports of the effects of phosphorus on the liver have been published. Its use began in the early days of experimental pathology and has continued to the present.

Wegner gave small doses of phosphorus to rabbits by mouth and continued the treatment through many months. This produced marked interstitial proliferation with nodular granulations in the liver. The illustration shows the gross characteristics of Laënnec's cirrhosis. Microscopically, perilobular fibrosis is shown, but there is no evidence of a distortion of the architectural pattern.

Dinkler found increase in connective tissue, proliferation of bile ducts and visible evidence of regeneration of hepatic cells following chronic phosphorus poisoning. Krönig compared the effects of acute and prolonged phosphorus poisoning in rabbits. Untreated litter mates of treated rabbits served as controls. Animals that died early showed only fatty degeneration and necrosis of liver cells. Beginning interstitial fibrosis, proliferation of bile ducts and evidences of regeneration of hepatic cells were found following phosphorus poisoning of longer duration.

Ackermann produced chronic phosphorus poisoning in rabbits. This was followed by perilobular connective tissue proliferation seen both macroscopically and microscopically. He regarded cirrhosis as the result of a defensive reaction of the tissue tending to counteract the effects of an injury—an early statement of a modern conception.

Aufrecht found diffuse inflammation and fibrous proliferation following phosphorus poisoning. The drawings that illustrate the article do not show whether a distortion of lobular pattern resulted.

De Josselin de Jong found periportal fibrosis, cellular infiltration and slight increase in the interstitial connective tissue in one rabbit which had been treated one hundred and twenty-nine days with phosphorus. Stolnikow reported degenerative changes in the liver followed by regeneration. There was no evidence of chronic hepatitis. Tischner found interstitial proliferation following phosphorus poisoning of long duration.

Paltauf reported 8 cases of phosphorus poisoning in man. The changes described in the livers of those who died between seven and fourteen days after the onset resembled closely those seen following death from acute yellow atrophy. Microscopically there was extensive parenchymatous and fatty degeneration, most marked about the periphery of the lobules. He noted visible evidences of hepatic cell regeneration from the biliary canals. There was young fibrous tissue proliferation in the perilobular spaces. He interpreted these changes as characteristic of early acute cirrhosis.

Fischler instituted an elaborate series of experiments on dogs, using a combination of phosphorus with amyl and ethyl alcohol. He found phosphorus combined with alcohol much more effective than phosphorus alone. He made a study of the function of the liver throughout these experiments by means of a complete biliary fistula. The presence of bilirubin or of urobilin was used as an indication of a disturbance of hepatic function. The treatment produced varying degrees of hepatic degeneration and secretional disturbance, resulting in marked fibrous tissue proliferation in the periphery of the lobules and leukocytic and mononuclear infiltration. He interpreted the fibrous proliferation and evidences of inflammation as a reparative process following injury. Photomicrographs show marked perilobular fibrosis and infiltration, with the lobular pattern distorted but not obliterated.

Balan found marked fatty changes in the liver but no cirrhosis following the use of phosphorus.

Mallory produced marked cirrhosis in rabbits and guinea-pigs by giving daily minute doses of yellow phosphorus with their food. After five months the livers were scarred, contracted and nodular, the condition closely resembling Laënnec's cirrhosis. Microscopically the cytoplasm showed the hyaline degenerative changes which according to Mallory are characteristic of "alcoholic" cirrhosis. He suggested that phosphorus as an impurity in iron or tin containers might, by the action of acids, become dissolved in alcoholic liquors. However, he failed to find any phosphorus in 25 samples of spirituous liquors tested. He stated that after thirty-six years of experimentation on alcoholic cirrhosis he, like other investigators, had ruled out ethyl alcohol as the cause. He had attempted unsuccessfully to produce cirrhosis with over 30 toxic substances which might possibly be present as contaminants in

alcoholic liquors. Photographs of the livers of the guinea-pigs present the marked nodular, granular, contracted features of Laënnec's cirrhosis (fig. 2). The photomicrographs show marked perilobular cirrhosis. There is moderate extension of connective tissue into the margins of the lobules but no distortion or obliteration of the lobular pattern.

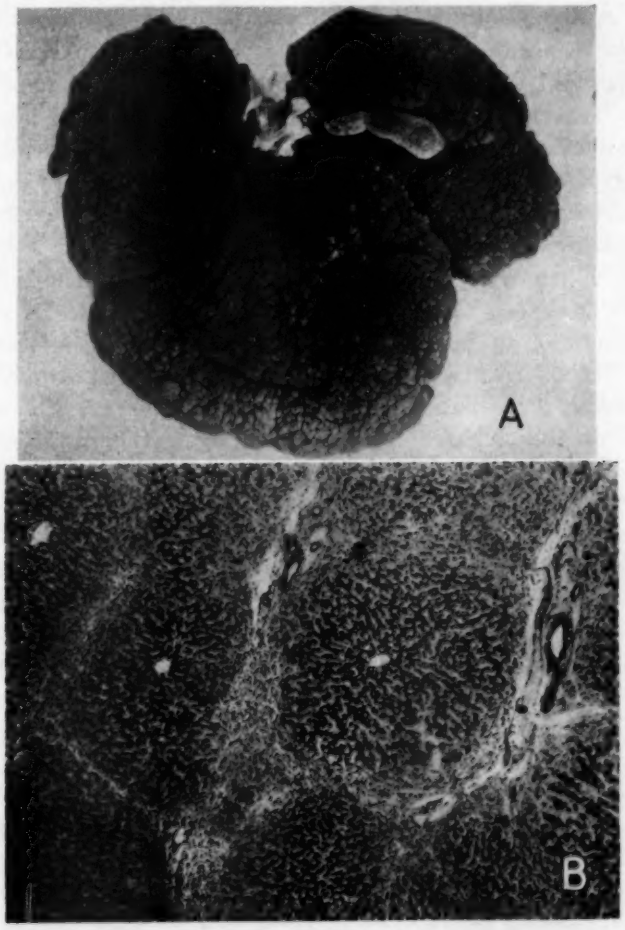

Fig. 2.—*A*, cirrhosis produced by phosphorus (Mallory). The gross features are indistinguishable from portal cirrhosis. *B*, photomicrograph of cirrhosis produced by phosphorus (Mallory). The cirrhotic process is marked, but the lobular pattern is not distorted. This does not reproduce the essential histologic feature of portal cirrhosis.

Arsenic.—One of the characteristic effects of arsenical poisons is the injury produced in hepatic cells. Necrosis results if the injury is severe. Ziegler and Obolonski reported the effects of small doses of

arsenic on dogs and rabbits. In dogs only parenchymatous changes were seen. Podwyssotzki found localized areas of necrosis in acute arsenical poisoning. Following chronic poisoning he saw proliferation of fibrous tissue. Wolko gave a solution of potassium arsenate subcutaneously to rabbits in experiments extending to forty days. He found marked proliferation of hepatic cells and bile ducts accompanied by leukocytic infiltration and proliferation of connective tissue in the periphery of the lobules and within the lobules.

Ehrlich made toxicologic studies on a huge series of arsenical compounds. He observed that degeneration and necrosis of hepatic cells were constant features of arsenical poisoning. This has been confirmed by Grote, Fischler, Sollmann and others. Fischler believed that a combination of arsenic with alcohol would prove as effective as phosphorus with alcohol in producing cirrhosis.

Only a few experiments on the pathologic effects of organic arsenicals have been found. Testoni gave from 1.5 to 10.58 cc. of a 10 per cent solution of solarson to rabbits by intravenous injection. The animals died in from two to one hundred and fourteen hours. In some of the livers there were striking parenchymatous changes associated with diffuse hemorrhage. In others only congestion and hemorrhage were seen. Heitzmann gave acetarsone (stovarsol) and treparsol (a product similar to acetarsone) in amounts of from 0.5 to 1.5 Gm. by mouth to rabbits and guinea-pigs. The animals were killed from three to sixteen days later. Diffuse fatty changes of liver cells and Kupffer cells resulted. Chronic effects were not studied.

It has been observed repeatedly (Kuczynski, Gilbergleit and Föckler, Choisser and Wilson, Meyer and Heubner, Bortin, McDonald and others) that arsphenamine and similar arsenicals occasionally produce acute poisoning in susceptible persons. When death results in such cases, severe necrosis of the liver is found. Often the condition of the liver is described as resembling acute yellow atrophy. O'Leary, Snell and Bannick reported two cases of portal cirrhosis following chronic arsenical poisoning. They regarded arsenical cirrhosis as a definite clinical entity of which their cases were representative. They cited similar phenomena recorded by other observers. Rolleston and McNee stated that arsenic appears to be capable of setting up cirrhosis of the liver.

Lead.—Litten reported necrosis of the liver following injection of lead chromate into the mesenteric vein.

Coen and D'Ajutolo reported early stages of interstitial hepatitis in rabbits following the use of lead acetate. This was accompanied by a hyperplastic pericholangitis with fibrous tissue proliferation. Potain, Prevost and Binet, and Annino found localized necroses and some inter-

stitial proliferation following chronic lead poisoning. Lafitte reported 6 cases of cirrhosis in man following chronic lead poisoning, with no history of alcoholism. He produced chronic lead poisoning in 4 rabbits. The experiments lasted from forty-two days to five months. Degeneration and necrosis of hepatic cells were followed by perilobular connective tissue proliferation and atrophy of hepatic cells. The livers were indurated and contracted. Albot gave lead carbonate and lead acetate subcutaneously and by mouth to rats, guinea-pigs and rabbits. Degenerative changes of hepatic cells followed by reticulosis resulted. In lead intoxication of long duration, he described a form of diffuse hepatitis with periportal fibrosis and atrophy of cells in central areas.

Lancereaux believed that potassium salts used in the manufacture of alcoholic beverages might be responsible for cirrhosis. He fed potassium sulphate and potassium bisulphate to dogs, rabbits, guinea-pigs and rats. The conditions and results of the experiments are not clearly stated. He argued from experimental evidence and clinical observations that wines which had been cleared with calcium sulphate were more productive of cirrhosis than other liquors. This explanation was refuted by Vallin, Rendu and others, whose observations did not corroborate those of Lancereaux. Clinical observations on cirrhosis related to alcoholism are not limited to the use of "plastered" wines. Spirituous liquors have been incriminated more than wines. Lancereaux' observations have lacked experimental confirmation.

Gye and Purdy gave intravenous injections of sublethal doses of colloidal silica to rabbits. Poisonous doses produced parenchymatous degeneration and necrosis in the liver, spleen and kidneys. Chronic poisoning with smaller doses produced extensive cirrhosis. The descriptions are confirmed by photographs, but neither the histologic descriptions nor the illustrations indicate that distortion or obliteration of lobular pattern resulted from the effects of colloidal silica.

Polson gave iron for periods of from three to four years to adult rabbits, maintaining a very high level of iron in their organs. No cirrhosis or pancreatic damage was produced. He concluded that it is unlikely that excess of iron is responsible for the hepatic and pancreatic changes found in hemachromatosis.

Hugenin, Nemours-Auguste and Albot studied the effects of thorium dioxide in a series of rabbits. A single large dose caused death in a few hours, with marked necrosis of hepatic cells. Smaller doses administered over a period of time resulted in various stages of hepatitis. In the more chronic cases this produced a form of cirrhosis. Deficiency of hepatic function was demonstrated by the galactose test. The illustrations show periportal fibrosis without disturbance of architectural pattern.

Scott and Helz fed sodium aluminum sulphate to 80 white rats in concentrations up to 2 per cent of their food. Protracted feeding produced no deleterious effects on growth or reproduction. The livers appeared normal and contained a normal amount of iron. No abnormal gross or microscopic features were seen in the liver or in other organs.

Bolliger and Inglis found that a single treatment with roentgen rays produced pathologic changes in the livers of dogs surgically exposed. The immediate result of such treatment was necrosis of hepatic cells, not only superficially but also in the deeper portions though in less degree. In the animals which survived such treatment jaundice and ascites developed, and examination of the livers showed proliferation of connective tissue.

Manganese.—Findlay gave repeated small doses of manganese chloride by injection or by mouth to rabbits, guinea-pigs and rats. Acute poisoning resulted in degeneration and necrosis of cells about the periphery of the lobules. Subsequently cirrhotic changes occurred which were first recognizable as fibrosis about the periphery of the lobules. Later the proliferating fibrous tissue invaded the lobules. The cirrhosis was monolobular, and Findlay regarded it as biliary in type. Jaundice occurred frequently. His numerous illustrations confirm the descriptions. Marked invasion of the lobules by fibrous tissue is shown. In some instances the lobules are distorted, but the lobular pattern is still recognizable.

Handovsky, Shultz and Staemmler treated rabbits with manganese chloride and with organic salts of manganese. These regularly produced degenerative changes of the hepatic cells and round cell infiltration. In some there was fibrous thickening about Glisson's capsule, which they interpreted as the effects of chronic poisoning, although they made no claims to the experimental production of cirrhosis.

Martin made similar experiments with manganese chloride on guinea-pigs. His attention was directed particularly to early minute cellular changes indicated by alterations in the chondriosomes. He emphasized the importance of these as indicators of early cellular damage. His experiments led to the conclusion that parenchymatous lesions precede interstitial changes in the cirrhotic process.

Hurst and Hurst studied the effects of manganese chloride, chloroform and phenylhydrazine hydrochloride on the livers of guinea-pigs and rabbits. Subcutaneous injections of any one of these substances in quantities of from 0.15 to 0.25 Gm. per kilogram caused severe intoxication ending in death within twenty-four hours. In such cases extensive necrosis of the liver was present. Smaller doses repeated three or four times weekly produced extensive fibrosis of the liver. With chronic manganese poisoning cirrhosis developed more readily in rabbits than

in guinea-pigs. The condition of the liver was similar to human monolobular cirrhosis. A chronic inflammatory reaction was evidenced by cellular infiltration and by proliferation of bile ducts and connective tissue. Photomicrographs of such livers show that the lobular pattern was not destroyed, but in some instances the fibrosis was rather diffuse throughout the lobules. The injection of living colon bacilli into the portal circulation during the course of manganese poisoning in guinea-pigs markedly increased the severity of the cirrhotic process. Fibrosis was stimulated, resulting after a comparatively short time, in an intense cirrhosis resembling that of Laënnec. They found also that injections of manganese chloride were more effective in producing cirrhosis when combined with injections of phenylhydrazine. Photomicrographs of the livers following this treatment show unmistakable distortion and destruction of lobular pattern.

One object of their experiments was to observe degenerative changes in the brain, especially those in the lenticular nucleus, associated with hepatic cirrhosis. No such changes were found in their animals.

Rao found that manganese fed to rabbits led to necrosis in the periphery of the lobules in cases of acute poisoning. Small doses repeated over a period of time resulted in cellular proliferation, increase in collagen fibers, and other inflammatory changes in the periportal connective tissue. This produced a form of monolobular cirrhosis which he did not regard as similar to Laënnec's cirrhosis.

Albot found degeneration and proliferative changes having the nature of a diffuse hepatitis in guinea-pigs and rabbits following injections of manganese chloride subcutaneously. Van der Schueren reported marked degeneration of hepatic cells and slight periportal sclerosis in manganese chloride poisoning in guinea-pigs.

Copper.—Mallory, Parker and Nye reported the effects of prolonged feeding of copper acetate to animals. They found that this was followed by a chronic lesion of the liver in which heavy pigmentation was combined with cirrhosis. Rabbits and rats were more susceptible than guinea-pigs and monkeys. In from six to twelve months the condition of the liver in the rabbits resembled human hemachromatosis. Three cases of cirrhosis developed among 22 rabbits treated with copper. They believed that copper contained in food or drink is an important cause of hemachromatosis, and that alcohol accentuates the effects of copper.

Hall and Butt gave copper acetate by mouth or by injection to rabbits, rats and sheep, and found that it caused a marked increase in the copper content of the liver. They reported that the storage of copper in the liver was paralleled by a storage of hemofuscin which contained iron in a masked form. This, they and Mallory believed, was slowly

converted into hemosiderin, perhaps after some years. Alcohol given with copper acetate did not hasten or increase the deposit of pigment. Pigmentation was followed by fibrosis, producing a condition resembling early hemachromatosis. This was more marked in rabbits than in other animals. They did not believe that copper occurs in human food or drink in sufficient quantities to produce this effect.

Flinn and Von Glahn attempted the production of pigmentary cirrhosis by giving copper, but without success. They attributed the pigmentation reported by others in such experiments to the deposit of pigmented lipoids derived from exogenous sources such as vegetables in the diet, especially carrots. They found no difference in animals given sodium acetate as compared with those given copper acetate.

Polson gave copper acetate to rabbits as described by Mallory. He found 1 rabbit with cirrhosis among 18 that were treated with copper. A control group were fed on mangel-wurzels and turnips and given no copper. He reported a deposition of hemofuscin in the liver in 87.5 per cent of these.

Adrianoff fed rats organic and inorganic copper compounds. One series of rats were given from 1 to 20 mg. of copper sulphate in their daily diet. After from nine to fifteen months several of the animals showed an annular type of cirrhosis with proliferation of bile ducts. Animals fed copper plus alcohol or copper plus olive oil showed no greater tendency to cirrhosis than those fed copper alone. Other groups of animals were fed copper acetate, copper oleate, copper-lead stearate copper-aluminum oleate, aluminum stearate, iron stearate and bismuth stearate. One rat fed lead stearate showed moderate cirrhosis. No cirrhosis was found in any of the others in the series. He believed the inorganic salts of copper were more effective than the organic compounds.

Oshima and Siebert fed copper sulphate to rabbits over a period of eight months. The livers of these animals contained about sixteen times the normal content of copper. No cirrhosis was produced.

Herkel reported the effects of prolonged feeding of various copper salts to rabbits and rats. This produced storage of copper in the liver but no demonstrable evidence of pigmentation or of cirrhosis.

Mallory and Parker extended their former series of experiments and demonstrated that copper is stored in the liver and may be demonstrated there within twenty-four hours after its injection. They used guinea-pigs, rabbits, monkeys and sheep, and injected a 20 per cent suspension of metallic copper in lard subcutaneously. They found that acute poisoning with copper produced anemia, hemoglobinuria, pigmentation and necrosis of hepatic and renal cells. They believed that the

pigmentation of the liver was derived from the destruction of hemoglobin. Repeated injections produced a form of pigmentary cirrhosis resembling hemachromatosis.

Schindel fed copper sulphate with and without alcohol to rabbits and rats. There was marked accumulation of copper in the livers in experiments lasting one hundred and seven days, and in longer experiments there was pigmentation of the Kupffer cells. No cirrhosis resulted.

Hall and MacKay confirmed their previous results and those of Mallory, Parker and Nye by a carefully controlled study of the effects of copper acetate in rabbits. For each animal that received copper, a litter mate of the same sex was used as a control. It was given the same diet with copper omitted; vegetables containing carotene were excluded from the diets. Twenty-one rabbits received a diet containing 2 mg. of copper acetate per gram of food. The experiments lasted from twenty-one to one hundred and five days. Seventeen of the copper-fed animals showed hemofuscin pigmentation in the Kupffer cells, and 9 showed, in addition, cirrhosis of the liver. Five showed varying degrees of necrosis but no cirrhosis. None of the control animals for this group, and none of another group of animals receiving sodium acetate instead of copper acetate, showed pigmention or cirrhosis. The cirrhosis was perilobular, and the lobular architecture was not obliterated.

In another experiment 22 rabbits were fed diets rich in carrots, from thirty-two to fifty days. Three presented Kupffer giant cells which contained a moderate amount of hemofuscin, 1 early cirrhosis, and 2 slight connective tissue proliferation. This, perhaps, is not a higher occurrence of hepatic changes than should be expected in rabbits.

Villaret, Bertraud, Justin-Besançon and Even injected acetates of cobalt, copper, manganese and nickel into guinea-pigs and rabbits. The livers showed degenerative changes followed by a gradual increase in fibrous tissue. The sclerosis was evident about the third or fourth month. Pigmentation was not noted in this series.

It appears that many inorganic poisons are capable of producing degeneration and necrosis of hepatic cells, and that the prolonged effects result in reparative processes of a cirrhotic nature. Moderate distortion of lobular pattern was produced in animals other than rabbits by the use of phosphorus plus alcohol (Fischler) and by manganese chloride (Findlay). Marked distortion of pattern was produced by Hurst and Hurst with a combination of injections of manganese chloride and intraportal injection of colon bacilli. The relationship between copper and pigmentary cirrhosis is not clearly established, since there is absence of general agreement in the evidence. It seems improbable that inorganic poisons, with the possible exception of arsenic compounds, constiture an important factor in the etiology of human cirrhosis.

ORGANIC SUBSTANCES

A wide variety of organic chemicals and substances of protein composition have been used experimentally with resulting damage to the liver. Immune serums and anaphylactic reactions have resulted in necrosis of hepatic cells. In some instances such damage has been slight; in others it has resulted in chronic inflammatory changes. Varying degrees of fibrosis up to marked cirrhosis with obliteration of lobular pattern have been reported.

Alcohol.—The belief that cirrhosis is due to alcoholism has led to numerous experiments on the effects of alcohol. For a complete summary of experiments made prior to 1911, the reader is referred to reviews by van Heukelom, Klopstock, Poggenpohl, Saltykow and Fischler. Rössle's recent treatise on inflammations of the liver presents a conservative summary of experimental results from the use of various agents including alcohol. The following results are summarized from the review of Saltykow, whose attitude is sympathetic toward the experimental production of cirrhosis with alcohol. Dahlstrom Duchek, Joffroy and Serveaux von Baumgarten and Reiter [2] found no effects in animals following treatment with alcohol.

Kremiansky, Ruge, Challand, Pupier, Strassmann, Afanassijew, Kublin, Magnam, Mairet and Combemale, Tobaldo, von Kahlden, Inghilleri, Jovine, Friedenwald, D'Amata, Lafitte, Dujardin-Beaumetz and Audige, and Grandmaison [2] found varying degrees of degenerative changes with or without slight or moderate infiltration about the portal structures. Most of these inflammatory changes were found in rabbits. Those credited with producing marked interstitial proliferation, amounting to cirrhosis, were Strauss and Blocq, De Rechter, Mertens, Saltykow and Fahr. The results obtained by these workers, whose reports are quoted frequently, and the experiments subsequent to 1911, will be reviewed briefly.

Strauss and Blocq gave mixtures of ethyl and amyl alcohol daily to 24 rabbits through a stomach tube. Most of the rabbits died within three months. Parasitic lesions were noted in the livers of several. There were no other significant findings. Two lived seven and one-half and twelve months, respectively. Both showed marked perilobular lymphocytic infiltration and proliferation of young connective tissue, which was interpreted as early cirrhosis. The illustrations indicate chronic periportal inflammation; the lobules appear normal, and there is no distortion of pattern.

De Rechter used 10 rabbits and 3 dogs. These were given a mixture of ethyl alcohol, 22.5 per cent, amyl alcohol, 2.5 per cent, water, 75 per

2. For references to the original articles of some of these authors, the reader is referred to the reviews by Fischler, Saltykow, and others.

cent, by stomach tube. Several animals died early in the experiment. The report is based on 2 rabbits which lived five and a half and nine months, respectively, and 1 dog which lived twenty weeks. The livers of the rabbits were described as firm, fibrotic and granular with a perilobular increase in connective tissue. Periportal fibrosis was seen in the dog's liver. The report is indefinite and is illustrated with diagrammatic drawings. These do not show distortion of lobular pattern, and the evidence of cirrhosis is inconclusive.

The report of Mertens is frequently misquoted, and in many libraries his original article is not available, hence special attention is given to his experiments. Mertens gave chloroform mixed with paraffin by subcutaneous injection to 15 rabbits. The doses ranged from 0.25 to 0.5 cc. of chloroform given at intervals of from three to ten days. The experiments extended from six days to three and one-half months. Parasitic lesions of the liver were noted in several rabbits. The acute effects of chloroform on hepatic cells were marked granular degeneration, vacuolation, fatty degeneration and chromatolysis. The chronic effects were cirrhotic. He concluded that the results proved indisputably "that the administration of chloroform in small doses continued over a long time produced in rabbits a disease presenting all the characteristics of Laënnec's granular atrophy of the liver in man."

In another experiment 12 rabbits lived from twenty-five days to eleven months in an atmosphere charged with alcohol by evaporation. Several died early with evidences of parasitic disease. Details are given of the gross examination of each rabbit, but the microscopic observations are recorded in general, without reference to individual animals. He stated that in some the liver was firmer than normal, that there was an abnormal proliferation of connective tissue in the portal spaces, and that ascites was abundant. One notes that in 5 of the 12 rabbits there was fluid in the peritoneal cavity described as clear in some and as flocculent or purulent in others. In several instances the presence of this fluid coincided with the presence of parasitic lesions in the liver. In no instance was the fluid associated with a liver having cirrhotic characteristics. He found varying degrees of cellular degeneration and some inflammatory reaction accompanied by leukocytes and proliferating fibrous tissue in the periportal areas. He made no claim for the production of cirrhosis by alcohol.

The article is illustrated by thirteen figures, eleven of which show the effects of chloroform and support adequately the author's conclusion that they resemble Laënnec's cirrhosis. For the animals which received alcohol only two drawings are presented. These show hepatic cells in high magnification and illustrate degenerative changes only. In one a multinucleated giant cell is represented. No proliferation or inflamma-

tory changes are shown. Parasitic disease was prevalent among Merten's rabbits. In only 2 of the alcohol-treated rabbits was it stated that no parasitic lesions were seen. Disregarding coccidiosis, one would conclude that the experiment with chloroform resulted in marked cirrhosis. Likewise one would conclude that in the experiment with alcohol no acceptable evidence of cirrhotic change was shown.

Saltykow gave minute doses of alcohol diluted with saline solution intravenously to 3 young rabbits. Two died soon and their organs showed nothing significant. The third rabbit lived two years and seven weeks, having received in eight doses a total of 2.5 cc. of absolute alcohol. One month following the last injection the rabbit became severely ill and died fourteen days later. Marked cirrhosis and arteriosclerosis were found in this rabbit. Apparently Saltykow regarded this experiment as significant.

Fahr fed alcohol to 3 rabbits and 2 guinea-pigs for periods extending to three years. Marked fatty changes of the liver resulted. The liver of 1 rabbit showed fibrosis, but Fahr was not convinced that it should be interpreted as cirrhosis. He stated: "The cardinal symptom of chronic alcohol poisoning is fatty change of the liver. This may or may not be accompanied by inflammatory changes."

The details of one significant experiment with negative results will be given. Under the auspices of the Committee of Fifty, Friedenwald made an extended investigation on the effects of alcohol in animals. This was given in the form of whisky or of absolute alcohol suitably diluted, by stomach tube, to 120 rabbits. Acute alcoholic poisoning lasting a few days and chronic effects of more than four years' duration were studied. One rabbit received 14,925 cc. of absolute alcohol. Each of 49 animals received more than 1,000 cc. of alcohol. One rabbit received 18,751 cc. of whisky. Twenty-three rabbits received over 1,000 cc. of whisky. A great majority of the animals showed fatty changes of the liver, heart and kidneys. These effects were temporary. They were not found in the animals whose treatment with alcohol had been discontinued a short time prior to their examination. In 1 rabbit cirrhosis with ascites was found; this was not regarded as significant in so large a series of animals. The evidence from this experiment was reviewed and verified by William H. Welch, who agreed with Friedenwald in the conclusion that such lesions as cirrhosis, chronic nephritis or arteriosclerosis had not resulted.

The review by Saltykow would be misleading to those unfamiliar with the original reports. It contains inaccuracies of statement, and the reviewer speaks *ex parte*. An attitude of objectivity toward the evidence is lacking. Fahr is credited with producing cirrhosis, which Fahr did not claim. Merten's results are interpreted as the successful

production of cirrhosis with alcohol and are defended with argument. Saltykow's result with 1 rabbit is stressed, but no mention is made of the conditions and results of Friedenwald's experiment on 120 rabbits. Coccidiosis as a factor in various experiments in which cirrhosis occurred is lightly set aside. The review summarizes the effects of alcohol on various organs and emphasizes its cirrhotogenic action.

Bischoff gave whisky in quantities of from 10 to 20 cc. daily to young rabbits through a stomach tube. The treatment continued from three to seven weeks. Marked fatty infiltration of the heart and liver resulted. This was especially marked in the central portion of the lobules. The kidneys showed no effects. No changes resembling cirrhosis were found.

In Schafir's experiment, 22 rabbits received whisky by stomach tube; 9 rabbits received weekly intravenous injections of from 0.1 to 1 cc. of absolute alcohol suitably diluted; and 10 rabbits, receiving whisky by stomach tube, were given egg yolk and milk in their diet. Degenerative changes and fatty infiltration occurred in the first group, also localized areas of connective tissue proliferation and infiltration by small cells. The statement that these changes occurred in individual animals without relation to the length of treatment indicates that some process not related to the treatment caused them. The second group showed similar changes, described as more marked, and in the third group fatty infiltration predominated. Biopsy specimens of the liver were taken from a few rabbits in each group prior to treatment, for comparison of the condition before with that subsequent to treatment. Most of the rabbits died of intercurrent infections. It was not stated how many died, how long treatment of the survivors was continued, or how much alcohol was given. The observations were recorded in general, without reference to individual animals. Fatty changes and increase in stroma similar to those found in the liver in alcoholism were described. The author stated that no marked interstitial changes resulted. Photomicrographs at high magnification illustrate degenerative and fatty changes, and do not show cirrhotic characteristics.

Lissauer reported the results of injection of 50 per cent alcohol and of brandy intravenously into rabbits. The number of animals and the duration of treatment were not stated. In 1 rabbit the liver was firm and nodular. Microscopically there were infiltration and fibrosis about the markings of the lobules. No illustrations were given. He refrained from drawing conclusions from this experiment.

Kryle and Schopper gave alcohol intravenously, subcutaneously and by mouth to 34 rabbits. The rabbits lived from one day to thirteen weeks. Parenchymatous degeneration occurred generally. Marked fatty degeneration was seen in 10. Slight infiltration by small cells was noted in 7;

in 6 this was outstanding and was accompanied by proliferation of connective tissue interpreted as "beginning cirrhosis." In 3 they regarded chronic inflammation as "genuine cirrhosis." Many animals died early. The rabbit which survived longest received in thirteen weeks 870 cc. of 50 per cent alcohol. The liver showed beginning cirrhosis. Drawings furnished as illustrations show degenerative changes and varying degrees of chronic perilobular inflammation.

Isobe treated 80 rabbits and 7 dogs with alcohol and potassium sulphate, singly and in combination. The experiments extended from one to twenty months. In many of the animals there were severe parenchymatous degeneration and fatty infiltration. A few showed

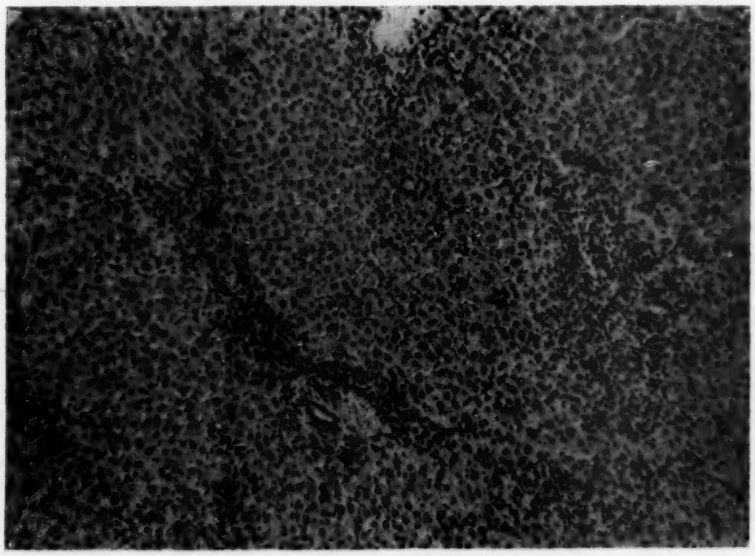

Fig. 3.—Photomicrograph of liver from an untreated rabbit. This type of chronic periportal inflammation is common among adult rabbits. It may easily be mistaken for "beginning cirrhosis."

round cell infiltration and moderate fibrosis of Glisson's capsule. The descriptions indicate a moderate chronic periportal inflammation. No illustrations are given.

Grover fed alcohol to rabbits for periods of from three to twelve months. He reported cirrhosis in varying degrees in 6 of the 12. His description of the microscopic changes indicates varying degrees of infiltration and of fibrous proliferation about the portal canals. The photomicrographs show moderate perilobular fibrosis such as is often seen in old rabbits (fig. 3). There is no distortion of lobular pattern. He credited Fahr with producing cirrhosis with alcohol, misquoted the

results of Afanassijew, Mertens and others, disregarded the experiment of Friedenwald, and concluded that cirrhosis can be obtained with alcohol independent of other factors.

Ogata gave alcohol to rabbits by injection into the portal vein and into the ear veins. In some of the animals there was perilobular fibrosis accompanied by degeneration of hepatic cells. No conclusions were drawn.

Wallace made clinical studies on cases of marked alcoholic intoxication. In 17 such cases the van den Bergh test for hepatic function showed a marked increase in urobilinogen and bilirubin. Urobilinogen was found also in the urine. He concluded that in acute alcoholic poisoning there is evidence of hepatic damage proportionate to the severity of the poisoning.

Rosenthal's experiments did not confirm Wallace's results. He found no increase of urobilin in the urine or of bilirubin in the blood following acute alcoholic poisoning in dogs. He found, however, that alcohol greatly increases the severity of chloroform poisoning in dogs. A two hour period of anesthesia from chloroform was fatal to 6 of 10 dogs previously intoxicated with alcohol given by mouth in a dosage of 2 cc. per kilogram of body weight. The livers of these dogs showed marked diffuse necrosis resembling that of acute yellow atrophy in man. In 10 dogs anesthetized two hours with chloroform but given no alcohol no fatalities resulted.

Adrianoff and Ansbacher mixed alcohol with food given to rats. The alcohol was in a concentration of from 20 to 50 per cent. In experiments lasting from nine to fifteen months no evidence of cirrhosis resulted. Van der Schueren gave 50 per cent alcohol in doses of 2 cc. per day to guinea-pigs during a period of from fourteen to seventeen months. He commented on the scarcity of resulting lesions. Two of the animals showed fatty degeneration of the liver. In 1 guinea-pig slight increase of connective tissue and mononuclear infiltration about the portal structures were seen.

MacNider reported hepatic changes resulting from acute alcoholic intoxication in dogs. Degenerative changes were produced in the cells in the outer zone of the lobules. These consisted of edema accompanied by an accumulation of lipoids. No necrosis resulted. In prolonged intoxication all portions of the lobules were involved. The cells returned to normal following such intoxication. Chronic effects were not studied.

No cirrhosis has been reported in experiments with alcohol in animals other than rabbits. Several authors stated that in dogs, rats guinea-pigs, etc., the liver is much more resistant, basing their conclusion on the results in rabbits. Some even claimed that rabbits are especially

suitable because of the ease with which fibrosis can be produced in their livers! Many of the illustrations and descriptions indicate the type of chronic periportal inflammation often found in the livers of old rabbits (fig. 3). Frequently the acknowledged presence of parasitic lesions in the livers was disregarded. Some authors have shown a non-critical attitude toward their results, and a few have appeared in the rôle of prosecuting attorney rather than in that of unprejudiced judge.

Without minimizing the contributory or predisposing influence which alcohol may exert, it must be concluded that experimental evidence has not substantiated the belief that alcohol is a direct cause of cirrhosis. Combination of alcohol with other agents has greatly increased their toxic effects on the liver. Fischler's experiments with alcohol and phosphorus, Scagliosi's results with alcohol plus bacteria, Wallace's results with alcohol plus chloroform and the results of Lamson, Wing, Mann and others with alcohol plus carbon tetrachloride are instances of the contributory effects of alcohol. It is probable that such influence as alcohol exerts in causing human cirrhosis results from its action in reenforcing or accentuating the effects of other agents or in producing degenerative changes in the hepatic cells, thereby rendering them more susceptible to injury.

Chloroform.—Merten's experiment with chloroform is described under experiments with alcohol. Herter and Williams gave chloroform by inhalation to 4 dogs. The experiments lasted from six weeks to eight months. They reported marked cirrhotic changes, but gave no precise histologic details and no illustrations of the changes seen.

Fiessinger intoxicated rabbits with chloroform by injection after the method of Mertens. He studied the stages of injury, degeneration, regeneration and repair which led to cirrhosis. He found that livers injured by chlorofrom, toluylene diamine and other substances showed two phases of reaction: (1) a parenchymatous phase evidenced by degeneration and necrosis followed by regeneration and (2) a later phase of fibrous tissue proliferation leading to scarring.

Whipple and his associates studied the effects of diet on the regeneration of hepatic cells following chloroform poisoning. They found that a diet of carbohydrates and milk was most favorable for repair of the liver following chemical injury. Gelatin was found as effective as casein in facilitating repair following a unit injury by chloroform.

Opie and Alvord found that injurious effects of chloroform and of phosphorus on the liver were greater in dogs on a diet of meat than in those on a mixed diet. Also chloroform intoxication produced more extensive necrosis of the liver and more serious systemic disturbances if the animals were given a diet rich in fats. The effect of chloroform was minimized by a diet high in carbohydrates. These observations

have been substantiated by those of Mann on the influence of diet in experimental cirrhosis produced with carbon tetrachloride.

Jaffé produced hepatic damage resulting in what he considered cirrhosis by subcutaneous injections of chloroform and of amyl alcohol in rabbits.

Schultz, Hall and Baker injected chloroform directly into the portal vein in a series of 80 dogs. This produced immediate necrosis of hepatic cells in the periphery of the lobules. Frequently extensive groups of lobules were destroyed. Very prompt mobilization of phagocytes occurred. These appeared to be engaged in removing the débris. Simultaneously fibroblastic proliferation occurred. The areas of necrosis were repaired by regeneration of hepatic cells accompanied by proliferation of bile ducts and by fibrosis. Following such repair the livers were contracted, firm, tough and nodular, and cut with increased resistance. There were heavy bands of connective tissue. Marked cirrhosis was produced, which they stated resembled true (Laënnec's) cirrhosis only superficially.

Macchiarulo reported on the effects of chloroform and of chloroform plus cholesterol given to rabbits. Marked parenchymatous and fatty degeneration followed by periportal fibrosis resulted. He found that chloroform plus cholesterol was more effective in producing hepatic damage than chloroform alone. No illustrations are given.

Tar.—Murayama reported cirrhotic changes in the livers of rabbits treated with tar for the experimental production of skin cancer. Later he reported on the injection of tar and of tar plus hydrous wool fat and of the latter alone into the peritoneal cavities of rabbits. Marked hepatic changes which grossly resembled granular cirrhosis were found in the animals given injections of tar and of tar plus hydrous wool fat. These changes were not seen in those receiving hydrous wool fat alone. The fibrotic changes were such as to cause shrinkage of the liver. They were described as perilobular. No illustrations accompany the report.

Schirokogeroff noted marked cirrhotic changes in the livers of rabbits whose ears had been painted with tar for the experimental production of cancer. At his suggestion, Leitman investigated these changes by further experimentation. He painted the ears of 10 rabbits with a mixture of petroleum tar and toluene. These treatments were repeated at intervals of two days. After from two to three weeks the animals became anemic and lost weight. The experiments lasted from one to four months. Marked hepatic changes resulted in each of the 10 rabbits. In the experiments of shorter duration the liver was mottled, firm and finely granular, and cut with resistance. Microscopically it showed marked degeneration accompanied by connective tissue prolifer-

ation. In experiments of longer duration the livers were coarsely granular and contracted. A photograph of the liver presents the hobnail appearance of Laënnec's cirrhosis (fig. 4*A*). Photomicrographs show marked cirrhotic changes with evident distortion or destruction

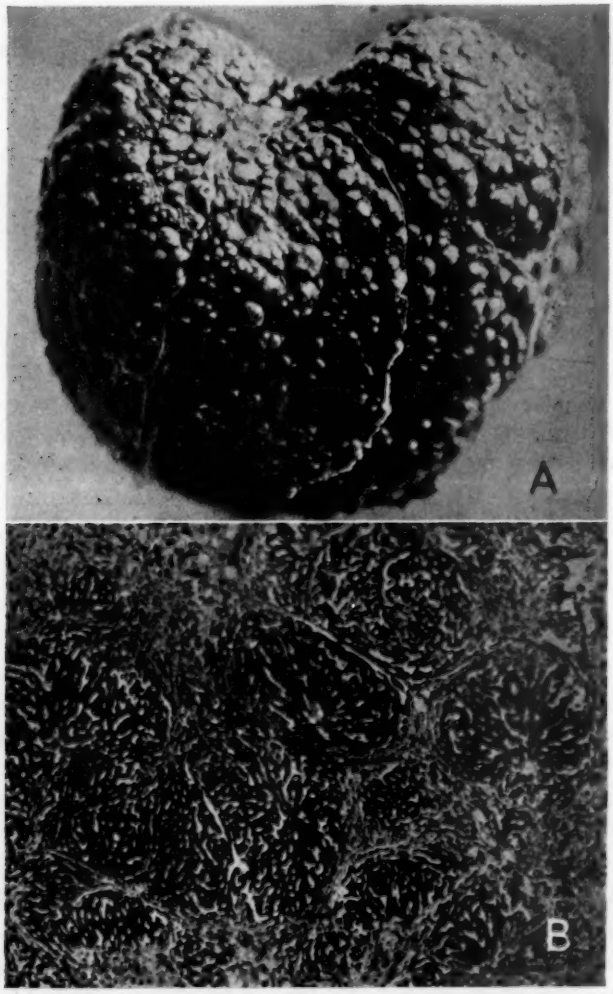

Fig. 4.—*A*, liver from rabbit treated with tar (Leitman). This liver presented both the gross and the microscopic characteristics of portal cirrhosis. *B*, photomicrograph of liver from rabbit treated with tar (Domagk). This shows marked distortion of the lobular pattern. "There are no longer lobules but only nodules of liver cells."

of the lobular pattern and with irregular areas of intercellular fibrosis. In 9 of the 10 the spleen was markedly enlarged and showed hyperplasia of the reticulo-endothelial tissue and hypoplasia of follicles.

Ascites was reported in 7 cases. Rabbits treated with toluene alone showed no such changes.

Davidson applied coal tar (pix liquida) to the ears of rabbits at intervals of a few days. Acute illness with marked loss of weight followed, ending in death within nineteen days. The condition of the liver resembled acute yellow atrophy. Extensive areas of necrosis and marked cellular degeneration accompanied by polymorphonuclear infiltration were present. Chronic effects were seen in rabbits which lived from two to five months following treatment. Abdominal ascites was present, and the liver was rough and nodular. Microscopically, proliferation of fibrous tissue surrounded areas of hepatic cells which were in varying degrees of degeneration and necrosis. There was proliferation of bile ducts with evidences of regeneration of hepatic cells. He believed that acute yellow atrophy, subacute yellow atrophy and cirrhosis are different stages in the same process. Photographs of gross specimens and of microscopic cross-sections substantiate the author's description. Distortion of lobular pattern characteristic of Laënnec's cirrhosis is shown.

Domagk applied tar to the ears of rabbits in attempts to produce cancer. The animals became cachectic. The livers were indurated and had roughened granular surfaces. There was a marked increase in fibrous tissue enclosing nodules of hepatic cells. His descriptions and photographs show marked distortion, if not obliteration, of the lobular pattern (fig. 4*B*). The condition closely resembled Laënnec's cirrhosis as seen in man. These results were found in each of 6 rabbits following the application of tar from fifty-seven to ninety-five times. In each instance there was atrophy of splenic pulp; ascites was reported in 4 of the 6 rabbits.

Polson gave shale oil in doses of from 2 to 10 cc. to rabbits subcutaneously, intraperitoneally, intrapleurally and *per vaginam*. Single large doses produced extensive hepatic necrosis. Hepatic damage in all stages from necrosis to cirrhosis resulted from repeated smaller doses. Cirrhosis having all the features of atrophic cirrhosis in man was reported. Each experiment was controlled by a biopsy on a specimen of the liver obtained by laparotomy before treatment of the animal. Photographs show a rough nodular condition of the liver resembling Laënnec's cirrhosis. One of the photomicrographs shows distortion of the lobular pattern.

Carbon Tetrachloride and Related Substances.—Fiessinger, Wolf and Blum subjected mice to an atmosphere charged with tetrachlorethane by evaporation for one and a half hours repeatedly. This produced stupor and other symptoms resembling those from alcohol or ether. The mice became jaundiced, the urine contained bile, and at autopsy the tissues were visibly icteric. The livers had a nutmeg-grater

appearance. After from three to four days nuclear and cytoplasmic changes were seen. The mitochondria became enlarged and coarse. Later they were transformed into fatty droplets, and the cytoplasm became homogeneous. Repair began about the seventh day. Regeneration of hepatic cells was followed by connective tissue proliferation and cicatrization in the periphery of the lobules. The authors emphasized this sequence in all toxic injuries of the liver.

Ottenberg and Abramson gave tetrachlorophenolphthalein and tetrabromophenolphthalein to dogs and rabbits in doses of from 0.3 to 0.4 Gm. per kilogram. This produced violent illness, evidenced by weakness, staggering, vomiting and frequent defecation. Death resulted within eight hours. Examination showed extensive necrosis, hemorrhage and disruption of the hepatic architecture. Chronic effects were not studied.

Gardner and his associates gave carbon tetrachloride to dogs and rabbits by mouth, by inhalation, by subcutaneous and intraperitoneal injections and per rectum. In every instance extensive central necrosis of the liver resulted. There were no other lesions of consequence. Regeneration and healing began three or four days after the intoxication. They found that the addition of alcohol to carbon tetrachloride greatly increased its toxicity. Healing of the degenerated areas was accompanied by marked central fibrosis. Their photomicrographs confirm the observations but do not show obliteration of the lobular pattern.

Midorikawa gave 0.05 cc. of carbon tetrachloride to rabbits by subcutaneous injection at intervals of from five to seven days. This resulted in pronounced parenchymatous degeneration, hydropic degeneration and fatty changes in the liver. Congestion, stasis and hemorrhages were also present. These changes were followed by round cell infiltration and by proliferation of hepatic cells, bile ducts and connective tissue. The formation of pseudolobules was reported. No illustrations accompanied this article.

Lamson and Wing gave carbon tetrachloride and alcohol, separately and in combination, to three series of dogs. The experiments extended from five to six months. The livers were greatly scarred, granular and contracted following chronic intoxication with carbon tetrachloride. The combination of carbon tetrachloride with alcohol was more effective than carbon tetrachloride alone. Alcohol alone produced no visible changes in the livers. No changes were seen in other organs. Microscopic examination showed distinct scarring and distortion of lobular architecture. The photomicrographs indicate that the lobular pattern was obliterated.

Albot produced cirrhosis in rats, guinea-pigs and rabbits by giving carbon tetrachloride by inhalation. After two hundred and thirty days there was marked proliferation of fibrous tissue with atrophy of hepatic cells resulting in marked distortion of architectural pattern.

Van der Schueren gave 0.25 cc. of carbon tetrachloride twice weekly to rabbits and guinea-pigs. Extensive cirrhosis resulted from four weeks' treatment. This was described as having the characteristics of Laënnec's cirrhosis, and led the author to conclude that degeneration and destruction of parenchyma are primary, and that regeneration and proliferation are secondary processes.

Mann, Bollman, Anderson, Fishback, Higgins, Lacquet, Love, Priestly, Stephenson and Williamson have experimented by means of successive removals of portions of the liver, chemical injuries, dietary influences, circulatory conditions and other factors affecting the liver. The chief purpose of these studies was physiologic, but their bearing on cirrhosis is important. Following the work of Gardner, Lamson and Wing and others, they adopted carbon tetrachloride as a toxic agent producing permanent damage to the liver more accurately and effectively than either phosphorus or chloroform.

To dogs of average size Bollman and Mann gave from 3 to 5 cc. of carbon tetrachloride by stomach tube twice weekly. Such doses produced necrosis of liver cells followed by regeneration and fibrosis. Following a single toxic dose it was found that the reparative processes began within twenty-four hours. There was marked infiltration in which polymorphonuclear cells predominated at first, and mononuclear cells later. Disintegrated hepatic cells were removed, in part, by phagocytosis and were replaced by multiplication of adjacent uninjured cells. Proliferation of fibrous tissue apparently occurred from that present about the portal spaces. Repetition of the injury gave rise to extensive scarring of the liver; hypertrophic nodules developed forming islands of hepatic cells without normal relationship to the blood vessels and to the biliary ducts. The lobular pattern became distorted as in typical Laënnec's cirrhosis. After marked cirrhosis had been established it continued to progress slowly without further administration of the poison. The gross and microscopic appearances of the liver showed close resemblance to Laënnec's cirrhosis. The liver was very nodular and granular, and the microscopic picture showed alteration of architecture with distortion of the lobular pattern.

Vascular changes resembling those of Laënnec's cirrhosis developed. The total blood supply to the liver was diminished, owing to the cicatricial constriction about the vascular terminals. Varices and collateral circulatory channels were formed. Hemorrhage occurred in the stomach and bowel, and voluminous ascites developed. Quantities of from 1,000 to 3,000 cc. were removed repeatedly from some of the animals by tapping. It was found that diet had a marked influence on the development of ascites. Little or no ascites formed if the dogs were fed with

syrup and other carbohydrates. When a high protein diet was substituted, ascites became marked. This was again absorbed when the dogs were given carbohydrates. This evidence corroborates the observations of Opie, Whipple and their associates on the influence of diet on hepatic repair. These findings led Mann and his co-workers to conclude that, at least in their animals, the formation of ascites is not conditioned entirely by obstruction to the portal blood flow.

They were unable to produce necrosis of hepatic cells with alcohol alone, but a combination of alcohol and carbon tetrachloride was more toxic than carbon tetrachloride alone. They found that the toxic agents were more effective when given to fasting than when given to well nourished animals. The exclusion of the portal blood from the liver by means of an Eck fistula rendered the liver ten times more susceptible to carbon tetrachloride than is the normal liver. Eck's fistula also decreased the regenerative capacity of the liver. Surgical removal of a portion of the normal liver was followed by prompt restoration of the liver to its normal volume. In dogs with Eck fistula such removal was not followed by restoration. Apparently the normal flow of portal blood through the liver aids in its resistance to injurious agents and its regeneration following injury. In human cirrhosis interference with portal blood flow probably renders the liver more susceptible to injury and less capable of regeneration.

When well advanced cirrhosis had been established by treatment with carbon tetrachloride, portions of the involved livers were removed surgically. This was followed by very deficient restoration as compared with that following similar operations on normal dogs.

Ligation of the common bile duct was performed on a series of dogs. This produced marked jaundice, which decreased after a few weeks. The cells of the parenchyma showed little, if any, atrophic or other change, but those bordering the bile ducts were deeply pigmented, and there was evident proliferation of bile ducts with slight increase of connective tissue about them. Infection played an important part in these experiments. When infection occurred following ligation of the duct, the formation of connective tissue was marked, and there was atrophy of the parenchymal cells. In such experiments when one or more lobes of the liver were removed surgically, the regenerative capacity was found to be greatly lowered.

Mann and his collaborators also found that the transplantation of the common bile duct into any portion of the gastro-intestinal tract or the anastomosis of the gallbladder to any portion of the gastro-intestinal tract was invariably followed by severe effects in the liver. The changes varied from moderate cholangitis to marked cirrhosis. The type of cirrhosis is not specified but it is assumed that it was biliary.

Mann emphasized three factors tending to prevent the restoration of the cirrhotic liver in experimental animals: extensive cicatrization of the liver, reduction of the blood supply and jaundice.

Miscellaneous Organic Substances.—Boix produced degenerative changes followed by necrosis and proliferation of fibrous tissue and bile ducts, resulting in what he regarded as cirrhosis. These changes followed the used of butyric acid, valerianic acid and acetic acid. His work is frequently quoted as significant since these are products which might result from gastro-intestinal dysfunction. If such dysfunction with the production of such acids were an important factor in the development of cirrhosis, it would seem that a higher percentage of cirrhosis should be found among those suffering from various gastro-intestinal disorders. De Josselin de Jong, D'Amato and others failed to produce cirrhosis by feeding butyric acid.

Poggenpohl mixed butyric acid with the food given to 6 rabbits over periods varying from thirty-two to one hundred and sixty-three days. He described a perilobular inflammation with a lymphocytic infiltration and a proliferation of connective tissue which he interpreted as the initial stage of interlobular cirrhosis. Chronic inflammation of the pancreas and catarrhal gastro-enteritis also were reported. The results are illustrated by drawings which indicate moderate periportal inflammation.

Inghilleri mixed fecal material from patients with hyperchlorhydria with the feed of rabbits. He reported chronic inflammation of the liver showing proliferation of connective tissue and of bile ducts. In another series he mixed the food with intestinal contents obtained from patients with hyperchlorhydria. This mixture was incubated forty-eight hours and fed to animals. Evidences of hepatic damage were reported as more marked in the latter than in the first group.

Chalatow mixed cholesterol with food given to 8 rabbits during periods of from fourteen days to four and one-half months. He found a pronounced deposit of anisotropic fats in the livers. Several of the livers showed an increase in fibrous tissue with cellular infiltration, and in one liver the condition resembled granular cirrhosis grossly and microscopically.

Hayami produced hepatic damage resulting in necrosis by injecting aleuronat into the portal veins. Healing of these lesions resulted in irregular scarring of the liver.

Adler mixed tobacco infusion with food given to rabbits. This produced interlobular accumulations of round cells followed in cases of long duration by a proliferation of fibrous tissue which occasionally penetrated slightly into the lobules. There was no distortion of the lobular pattern. Ogata injected an aqueous extract of tobacco leaves

into the ear veins of rabbits. Slight degenerative changes of the liver were seen but no fibrosis.

Rovighi and Portioli produced degeneration and leukocytic infiltration in the livers of rabbits by feeding them ammonium carbamate. Joannovicz confirmed these experiments with ammonium carbamate. He produced similar changes with toluylene diamine in dogs. This resulted in degeneration followed by proliferation of interlobular connective tissue and of bile ducts. Icterus was observed in some of the animals.

Hensen injected such poisons as chloroform, formaldehyde and sulphuric acid into the livers of cats by way of the bile ducts. Chloroform produced fatty changes and necrosis followed by restitution. Formaldehyde and sulphuric acid produced extensive necrosis followed by gradual resorption and regeneration. The regeneration and healing were accompanied by proliferation of connective tissue.

Krawkow mixed an infusion of putrid horse flesh with the food given to dogs for several weeks. He reported genuine cirrhosis following these experiments. He also injected cultures of Bacillus pyocyaneus into doves and observed cirrhotic changes in their livers.

Ignatowski fed milk, meat and eggs to young rabbits, and reported that the livers became cirrhotic. Ascites was present in 1 animal. His description indicates marked degenerative changes of the liver with periportal fibrosis. The spleen was regularly enlarged, and atheroma of the aorta and parenchymatous degeneration of the kidneys were reported. The drawings show periportal inflammation and proliferation of connective tissue, without distortion of lobular pattern.

Flexner produced intoxications of guinea-pigs and rabbits with bacterial protein, ricin, abrin and foreign serums, and found necrosis of hepatic cells followed by leukocytic infiltration fibrosis and proliferation of bile ducts in animals that survived several weeks. He stated that grossly the livers were firm and somewhat granular, but that they did not reproduce the gross or the microscopic features of human cirrhosis.

Deutsch prepared an antihepatic serum by immunizing rabbits against the hepatic substance of other animals. The injection of such serum into the peritoneal cavities of animals produced necrosis of the liver. Cantacuzene reported similar results. Delezenne injected antihepatic serum into the peritoneal cavities of dogs. The dosage was from 2 to 4 cc. per kilogram of body weight. This produced severe intoxication and death in from fifteen to twenty-four hours. The condition of the livers resembled acute yellow atrophy. In animals which survived from five to fifteen days there was marked inflammatory reaction with leukocytic infiltration and proliferation of fibrous tissue. This was accompanied by regeneration of liver cells. No illustrations accompany the

article. Joannovcz reported degenerative changes in the liver followed by regeneration and proliferation of fibrous tissue, resulting from injections of immune serums.

Fukuhara produced intoxication of rabbits, guinea-pigs, rats, dogs and hens by injecting foreign proteins, bile and hemolytic serums. Localized necroses of hepatic cells were found. Parenchymatous changes were seen in other tissue. The chronic effects of such agents were not studied.

Civray found that the injection of specific hepatolytic serum into animals caused acute degeneration, necrosis and cytolysis of hepatic cells. Other organs were affected in minor degrees. Chronic or repeated effects of such treatment were not studied.

Pearce gave dogs injections of serums from rabbits which had been immunized to dog's red blood corpuscles. Some of the dogs so treated died in from four minutes to forty-eight hours. In these there was diffuse necrosis of the liver. In the livers of those which lived forty-eight hours or longer, proliferation of endothelial cells and of connective tissue cells was seen. In five days there was marked regeneration of hepatic cells with proliferation of granulation tissue. In 1 dog thirty-six days after injection of the serum the liver was firm and had a finely granular surface. On section, distinct pseudolobulations were seen. Histologically there was marked perilobular fibrosis with lymphoid infiltration and proliferation of bile ducts. The reparative process was most active in the region of the portal spaces and resulted in diffuse cirrhosis. Illustrations show marked cirrhosis but no distortion of lobular architecture. Pearce did not claim that this experiment explained the origin of cirrhosis in man, but that it proved that cirrhosis results from a reparative process following parenchymatous injury.

Jaffé reported perilobular fibrosis in rabbits following repeated injections of a 10 per cent solution of hemoglobin.

Wells produced chronic perilobular inflammation which he described as cirrhosis, by subcutaneous injection of commercial peptone into guinea-pigs and rabbits. The livers were indurated, the fibrous tissue proliferation did not penetrate the lobules, and there was no distortion of the lobular pattern.

D'Amato gave rabbits and dogs injections of meat juices and broth. He reported marked congestion of the liver in each instance. In some there were degeneration and necrosis associated with round cell infiltration about the portal structures.

Longcope produced anaphylactic shock in dogs, cats, rabbits and guinea-pigs which had been appropriately sensitized to egg or serum albumin. Repeated anaphylactic intoxication resulted in necroses of groups of cells in the periphery of the hepatic lobules. The healing of

these resulted in a proliferation of scar tissue which was perilobular in location. There was no distortion of the lobular architecture.

Lissauer injected a sterile extract of horse flesh intravenously into 4 rabbits. Doses of 5 cc. of the extract were given at intervals of six days. The experiments lasted from thirty-four to seventy days. His descriptions and drawings indicate moderate perilobular hepatitis.

Apparently several compounds of the benzine series have the property of producing damage to the parenchyma of the liver. Iwanoff found marked parenchymatous and fatty degeneration of the hepatic cells following treatment with antipyrine. No fibrous tissue proliferation was reported. Marckwald produced local necroses of the liver by subcutaneous injection of antipyrine into frogs and rabbits. A marked perilobular fibrosis with proliferation of bile ducts resulted in what he regarded as a typical picture of cirrhosis.

Some significant observations concerning the effects of aniline, toluidine and methenamine have resulted from experiments not primarily designed to produce hepatic damage or cirrhosis. It had been noticed that those who work with aniline compounds frequently acquire primary neoplastic growths. Jaffé undertook an experimental investigation of this phenomenon. Groups consisting of equal numbers of rabbits, guinea-pigs and mice were given aniline, toluidine and methenamine in gaseous form by inhalation. The average duration of the experiments was six months; the longest duration was one year and four months. No neoplastic growths resulted in any of the animals, and no significant changes were seen except in the livers. The animals treated with aniline and those with toluidine showed marked parenchymatous and fatty changes of the liver. Those receiving methenamine presented necroses accompanied by regeneration of liver cells, round cell infiltration and proliferation of connective tissue. Jaffé saw in these results a relationship to the experimental production of cirrhosis.

In another experiment he reported cirrhosis in rabbits following injections of hydrazine sulphate and of phenol hydrazine hydrochloride. Large doses of these agents produced extensive necrosis of hepatic cells. Smaller doses repeated over long periods produced degeneration followed by marked connective tissue proliferation and lymphocytic infiltration. His illustrations confirm these findings, but they show no distortion of the lobular architecture.

Hurst and Hurst injected phenylhydrazine in doses of from 0.1 to 0.17 Gm. into rabbits and guinea-pigs. Some necrosis of hepatic cells followed acute intoxication with phenylhydrazine, but no distinct cirrhosis resulted from chronic intoxication with it. The injection of quantities of sheep bile or human bile into animals was not followed

by degeneration and fibrosis of the liver. Injections of guanidine likewise resulted in no hepatic structural changes.

Cinchophen.—Sherwood and Sherwood collected from the literature 48 instances of cinchophen poisoning in man, 15 of which ended fatally. It was noted that extensive hepatic necrosis is characteristic of cinchophen poisoning.

Churchill and Van Wagoner fed cinchophen daily to dogs in a dosage of 595 mg. per kilogram of body weight. The dogs died in from ten to twenty days. The livers showed areas of necrosis of varying extent. Prolonged treatment with cinchophen produced gastric and duodenal ulcers, but cirrhosis was not seen.

Reichle gave cinchophen subcutaneously to rats. A single dose of 1 Gm. per kilogram of body weight caused death within twenty-four hours. The liver, kidneys and spleen showed extreme degeneration and necrosis of cells. Doses of from 0.2 to 0.5 Gm. per kilogram of body weight were given daily for eight days. Marked illness and partial paralysis followed. The organs showed severe parenchymatous degeneration and focal necrosis. When the treatment was discontinued recovery followed. Seventeen days later the liver had returned to a normal histologic picture. The healing process was not accompanied by fibrosis. Similar results were obtained in rats when their livers had been depleted of glycogen by starvation.

Barbour and Fisk gave cinchophen, neocinchophen and sodium salicylate by mouth to groups of dogs and rats. Acute hepatic degeneration and necrosis resulted from the activity of each. They found that the order of hepatic toxicity from these drugs was cinchophen > sodium salicylate > neocinchophen. No cirrhotic changes following cinchophen were found in six weeks. Gastric or duodenal ulcers were found in 4 of 8 dogs receiving cinchophen; none were found following sodium salicylate or neocinchophen.

Beaver and Robertson, also Permar and Goering reported on cinchophen poisoning in man. They confirmed previous observations that cinchophen produces extensive necrosis resembling that of acute yellow atrophy. But important differences in the two conditions were emphasized. Cinchophen produces a form of atrophy of the liver in which there is marked retardation of regeneration and in which proliferation of fibrous tissue and of bile ducts is not seen.

The experimental studies and the postmortem observations in man indicate that cinchophen produces marked hepatic damage, but that this may lead to cirrhosis has not been shown.

Fischer reported "typical cirrhosis of the liver" resulting from the intravenous injection of ether in "leinol" into mice and rabbits. His report contains no histologic details and no photographs.

INFECTIOUS AGENTS

The belief that infections are important factors in the causation of cirrhosis has become rather general among pathologists. Mallory assigned infection as the cause for one group of cirrhosis. Beattie and Dickson stated that cirrhosis may occur secondary to infectious disease and regarded scarlet fever as of importance, especially in young subjects. Muir mentioned infection, especially scarlet fever, as important and stated that a fair proportion of cases are postinfective. Karsner included infection among the probable etiologic agents. Boyd believed that the major factor is probably a low grade bacterial infection. De Josselin de Jong found numerous authors in agreement that long-continued toxic or infectious processes were of primary importance. Fiessinger believed that infections are of major importance in tropical and subtropical countries. Yenikomshian found that cirrhosis is particularly prevalent in the rural population of Tyre and Sidon where alcoholic drink is taboo. A history of amebiasis or malaria was regular in such cases, and he believed that a combination of the two is the most important cause for cirrhosis in that population.

Wolff injected putrefactive bacteria subcutaneously into animals. This was followed by an interstitial hepatitis with round cell infiltration and connective tissue proliferation. In some of the animals this process was diffuse; in others it was localized and resulted in nodular lesions.

Roger found that experimental infections with streptococci or anthrax bacilli lowered the glycogen content of the liver and increased its susceptibility to injury. He produced interstitial hepatitis by repeated injections of "Bacillus septicus putridus."

Scagliosi produced beginning cirrhosis by repeated inoculation of nonpathogenic bacteria into alcohol-treated animals. Rabbits, guinea-pigs and chickens were used. He believed that alcohol acts as a "near cause" in producing hepatitis, a view which has found support among pathologists in recent years.

Dantschakow-Grigorevski injected broth cultures of staphylococci of low virulence into rabbits during periods of from seven to fifteen weeks. The number of animals was not stated. The livers of 2 were described as large and firm. Drawings illustrate periportal inflammation.

Brieger reported cirrhosis in rabbits and guinea-pigs following inoculation of tubercle bacilli. Hanot and Gilbert reported the production of cirrhosis following injections of tubercle bacilli of lowered virulence. Besançon, Griffon and others reported similar results from experiments with Bacillus tuberculosis. Joanovicz described the production of cirrhosis in guinea-pigs following the injection of urine from tuberculous kidneys. Ogata injected a sterilized suspension of tubercle bacilli into the portal veins of rabbits. This resulted in "tuberculous cirrhotic

changes." A sterile suspension of colon bacilli similarly injected produced slight inflammatory changes in the liver.

Adami investigated an epidemic disease of cattle which produced marked cirrhosis resembling that seen in man. He found in the livers numerous coccoid organisms which, when cultivated, resembled the bacillus of hemorrhagic septicemia. When inoculated into rabbits the organisms produced marked degeneration and necrosis of the liver. The animals died early before cirrhotic changes could occur. Adami regarded "sub-infection" as important in producing cirrhosis.

At this point attention is called to the frequent occurrence of cirrhosis in rabbits as a result of chronic coccidiosis and to its occasional occurrence in guinea-pigs as a result of an infection resembling tuberculosis. If spontaneous infections produce cirrhosis in animals it is probable that they may do so in man.

Flexner, whose work is referred to in another section, included bacterial substances among the injurious agents that produced cirrhotic changes in guinea-pigs and rabbits.

Kirikow cultivated diplococci from the liver in 4 cases of what he regarded as Hanot's cirrhosis. In each case the condition was acute and was accompanied by fever, icterus and enlargement of the liver and spleen. The liver was described as distinctly granular, containing nodules of hyperplastic cells. The organisms isolated were pathogenic for mice. Those which survived the initial inoculation were reinoculated repeatedly. This produced marked diffuse hepatitis, with inflammatory infiltration and fibrosis of the liver, accompanied by splenic enlargement.

Weaver reported the isolation from a spontaneously infected guinea-pig of a bacillus not definitely identified but belonging to the colon group. When inoculated into guinea-pigs this organism produced marked hepatic necrosis followed by death. Animals that lived seven days or longer presented cirrhotic changes. These consisted of regenerated liver cells and proliferation of bile ducts and of fibrous tissue. No illustrations are given. This organism became avirulent in artificial mediums.

Hektoen isolated from human blastomycotic lesions an organism which morphologically resembled Bacillus diphtheriae but differed from it in certain particulars. When cultures of the organism were inoculated into guinea-pigs, rabbits and dogs, it produced early death with marked degeneration, necrosis and acute inflammation of the liver. In animals that survived two weeks or more the liver showed inflammatory changes with perilobular fibrosis and proliferation of bile ducts. These cirrhotic changes were described as portal. Photomicrographs show marked cirrhosis with penetration of connective tissue into the lobules and with some distortion of the lobular pattern. The inoculated organism was recovered in subculture from the livers of some of the animals.

The organism became avirulent in later cultures, and subsequent experiments were without results.

Opie's experiments included combinations of toxic degeneration of the liver with bacterial infections. In one series he gave chloroform in amounts of from 0.5 to 1 cc. per kilogram to dogs at intervals. This was followed by marked degeneration and destruction of hepatic cells in the central portion of the lobules. Regeneration of the cells and proliferation of connective tissue and of bile ducts followed. In dogs that lived from two to three months, marked cirrhosis, jaundice and dilatation of the portal vein resulted. The fibrosis began about the central vein and extended into the lobules. Following repeated injury of this kind distortion of the lobular architecture resulted. Opie combined chloroform intoxication with intravenous injections of streptococci and colon bacilli. In animals examined at an early date this produced a picture resembling acute yellow atrophy. In animals that lived longer (twenty-three days) there was marked cirrhosis accompanied by proliferation of bile ducts. Photomicrographs show marked distortion of the architecture in some; in others the lobular pattern was visible. No ascites was reported in these animals.

Evidence indicating a relationship between infection and cirrhosis has been drawn from clinical observations and postmortem studies. In some instances such evidence has a significance second only to that of well controlled experimentation. A number of reports have indicated that streptococcic infections are related to the development of cirrhosis. Many of these were made before streptococci were known to be related to scarlet fever and measles.

Siredey described degenerative and inflammatory changes in the liver following diphtheria and also scarlet fever. He believed that such inflammation may become chronic and may account for the development of cirrhotic changes. He regarded alcoholism as a contributory factor making the patient more susceptible to infection.

In certain cases of scarlet fever and of measles Henoch found chronic lesions which constituted an interstitial hepatitis. He described marked degenerative changes associated with proliferation of bile ducts and of connective tissue. He regarded this as a form of hepatitis that might develop into cirrhosis.

Mogk reported the case of a child whose death from cirrhosis occurred eight weeks after a severe attack of scarlet fever. Streptococci were demonstrated in sections of the liver. The active process resembled those later described by Moon in similar cases.

Gastou described inflammation about the portal structures associated with diffuse hepatitis following acute infections. In such a liver from a child he found streptococci in chains. In 2 cases of cirrhosis, he

cultivated diplococci from the blood and from the hepatic substance. He believed various organisms caused infectious hepatitis which later produced cirrhosis.

Babes reported 4 cases of streptococcic septicemia which resulted in widespread degeneration and necrosis in the liver. Streptococci were cultured from the blood in each case, and similar organisms were found in microscopic examination of the liver. In 3 cases the condition of the liver resembled acute yellow atrophy.

Levi reported cirrhosis associated with mitral endocarditis in a boy 17 years of age. He cultivated from the liver a diplococcus which was pathogenic for guinea-pigs.

Bingel studied the liver in 8 cases of delayed death following scarlet fever. Extreme degeneration, necrosis of hepatic cells and perivascular inflammatory infiltration were found in every case. In the liver of one patient whose death occurred seven months after scarlet fever an advanced stage of cirrhosis was found. Bingel believed the cirrhosis in such cases to be a sequel of the infection.

Baginsky reported a case of streptococcic septicemia in a child. The liver showed interstitial hepatitis characterized by extensive degeneration and necrosis of hepatic cells and by a rather diffuse inflammatory reaction. Streptococci were cultivated from the blood stream and from hepatic substance obtained by puncture prior to death.

Rolleston and McNee included streptococci among the agents which may produce icterus gravis. It is generally believed that cirrhosis may develop from icterus gravis or from recurring attacks of toxic jaundice in which the etiology may be similar.

The occurrence of portal cirrhosis in children is not unusual, and it occasionally affects more than one in the same family. In such instances some acute infectious disease usually precedes. Howard reported 2 such cases of cirrhosis in a brother and sister aged 8 and 9 years. The disease developed following pertussis, and he included infection among the probable causes. Ely reported cirrhosis in twins 4 years old. The disease began with jaundice during an attack of measles and ended in death five months later. Moon reported 3 cases of cirrhosis in one family. Scarlet fever preceded the development of the cirrhosis. In 1 case hemolytic streptococci were cultivated from the substance of the liver at postmortem examination. A blood culture made a few hours prior to death was negative. This indicated that the streptococci found in the liver were not incidental to a terminal septicemia. The streptococci were inoculated into young rabbits by various routes. The animals lived from three to fifteen days, and in 11 of 12 rabbits the hemolytic streptococci were recultivated from the livers. Marked degeneration and necrosis and very little inflammatory reaction were present in the livers.

Moon and his associates cultivated streptococci from cirrhotic livers in 6 cases, and demonstrated cocci in sections in 9 others in which the cirrhotic process was active. Failure to cultivate or demonstrate organisms in a number of similar cases indicated that all were not due to the same cause.

MacMahon and Mallory reported 5 cases of streptococcic hepatitis, in 4 of which they demonstrated streptococci in the liver. Two were acute and showed degeneration and necrosis of hepatic cells with an associated inflammatory reaction. One was subacute, of six weeks' duration, and showed marked zonal necrosis affecting all the lobules. There was proliferation of hepatic cells and of fibrous tissue such as is characteristic of early cirrhosis. In another case the liver, seen during cholecystotomy, appeared normal, and an excised section had normal histologic features. Subsequently chills and fever developed, accompanied by jaundice. The liver became enlarged; ascites developed and was removed by tapping on two occasions. The condition progressed to a fatal termination eight and one-half months following the operation. Pronounced cirrhosis was found post mortem, and numerous streptococci were demonstrated in the liver. They regarded this as a chronic hepatitis due to streptococci of moderate virulence. This has caused a diffuse progressive destruction of hepatic cells resulting in cirrhosis. Guinea-pigs and rabbits, inoculated via the portal vein with Streptococcus scarlatinae, showed localized and diffuse areas of hepatic necrosis. Chronic effects were not studied. They believed that streptococci may cause hepatic necrosis resembling that of acute yellow atrophy, and that it may develop into cirrhosis.

In view of the fact that infections outrank all other agents in the production of chronic inflammatory processes, it is strange that they have received so little investigation as possible causes of cirrhosis.

OBSTRUCTION TO VESSELS AND DUCTS

Obstructions to the hepatic vessels have been produced experimentally by various means and in various combinations. These have resulted in circulatory, degenerative and atrophic changes in the parenchyma of the liver. No condition resembling portal cirrhosis has been reported from such experiments. Experimental obstruction to the hepatic duct produces pathologic conditions which vary somewhat depending on the duration and the degree of the obstruction and on the presence or absence of associated infection. Such obstructions have not produced portal cirrhosis, though the distinctive structural changes of biliary cirrhosis have been reproduced satisfactorily by such means.

No review of such experiments will be attempted since there is general agreement as to the origin and development of biliary cirrhosis.

Occasionally such a condition becomes progressive and the parenchymal injury is no longer limited to the periphery of the lobules. In such an instance extensive injury and repair may lead to obliteration of the lobular pattern and to obstruction of portal circulation. Thus in rare cases the characteristic features of portal cirrhosis may be superimposed on those of biliary cirrhosis.

SUMMARY

A review of experimental cirrhosis shows that numerous agents, most diverse in character, are capable of causing degeneration and necrosis of hepatic cells. These include various chemicals, both organic and inorganic, certain drugs and tarlike substances, foreign proteins and products of protein decomposition, bacterial products, immune serums and infections. The continued or repeated action of these agents has resulted in the production of chronic diffuse hepatitis, as indicated by degeneration and necrosis, by regeneration of parenchyma and by proliferation of fibrous tissue.

Probably the majority of these agents have no etiologic significance in the development of human cirrhosis. Yet the results of the investigations of their action have contributed greatly to an understanding of the mechanism by which cirrhosis develops. In every instance in which the prolonged action of an agent has resulted in some degree of cirrhosis the acute effects have been degeneration and necrosis of hepatic cells. Cirrhosis, like other chronic inflammations, results from parenchymatous injury followed by repair. If such injury is severe, continued or repeated, the repair will be accompanied by fibrosis. This evidence should tend to allay a controversy of long duration between certain groups of European pathologists.

A few agents which have met satisfactorily the rigid criteria for Laënnec's cirrhosis are phosphorus plus alcohol, manganese chloride plus phenylhydrazine, carbon tetrachloride, tars, bacterial infections and combinations of infection with other agents, as in Opie's experiments. Each of these has produced a distortion of the architecture of the organ, in which marked alteration of lobular pattern was evident. The islands of regenerated hepatic cells occurred as nodules rather than lobules, and indicated the type of circulatory disarrangement which is characteristic of Laënnec's cirrhosis. In Mann's experiments with carbon tetrachloride the circulatory disturbances resulted in portal circulatory obstruction, as indicated by ascites and by the development of collateral venous channels.

The belief that cirrhosis is caused by alcohol has not received experimental support. Without exception the agents which have produced cirrhosis experimentally have caused hepatic necrosis. Alcohol, even in large amounts and with long-continued use, has caused only parenchyma-

tous degeneration and fatty changes. These have not resulted in necrosis nor in permanent hepatic changes. However, the probability that alcohol acts as a contributing or predisposing factor has received experimental support. Alcohol has been found to accentuate the injurious effects of bacteria, of phosphorus, of chloroform and of carbon tetrachloride on the animal liver. It is probable that alcohol may similarly accentuate the effects of injurious agents on the human liver. By virtue of this property alcohol may be an important contributory factor in the development of human cirrhosis.

Cirrhosis resulting from treatment with tar has duplicated Laënnec's cirrhosis with remarkable accuracy. The gross and microscopic characteristics have fulfilled rigid requirements. The splenic changes have resembled those accompanying Laënnec's cirrhosis, and ascites has been an almost constant associated feature. The fact that the experiments were made on rabbits makes necessary a high degree of conservatism. However, the very high percentage of positive results makes it probable that coccidiosis was not concerned. In Polson's experiments erroneous conclusions were partially obviated by examinations of the livers prior to experimentation.

The injurious effects of hydrazine and similar organic chemicals and the production of cirrhosis by means of tars, have perhaps a deeper significance than is apparent. Many investigators have believed that various substances present incidentally in alcoholic liquors might be responsible for cirrhosis occurring among drinkers of those beverages. Many such contaminants have been investigated without significant results. The tarlike products or substances of the benzine series formed by the charring of casks used for the ageing of liquor have not been investigated. Liquors aged in charred casks contain visible quantities of a brownish substance dissolved from the semicharred wood. Such substances might produce effects similar to those of tars. Is it possible that such substances may be responsible for the development of cirrhosis in habitual drinkers of alcoholic liquors?

There is evidence that metabolic disturbances may be important contributing factors. Medical literature contains record of many observations on the simultaneous occurrence of exophthalmic goiter and cirrhosis (Marine, Goodpasture, Raab and Terplan, Weller, Assmann, Haban, Beaver and Pemberton). Moon's survey on the occurrence of cirrhosis in different sections of the United States showed a most suggestive relationship between cirrhosis and thyroid disease. The states having the highest death rate from thyroid disease had also the highest death rate from cirrhosis and vice versa. A similar relationship is exemplified in European countries. The highest occurrence of cirrhosis on record is in Switzerland, where goiter also is most prevalent. Livers

with low glycogen content have an increased susceptibility to injury. Hyperthyroidism may contribute to the development of cirrhosis by producing hepatic glycopenia. Rössle and others have shown that marked thyrotoxicosis produces extensive hepatic necrosis. Hence thyrotoxicosis may be a direct cause of cirrhosis.

Infections in animals are known to cause a hepatitis which resembles Laënnec's cirrhosis closely. The experiments of Weaver, Hektoen, Opie, Mallory and others have been cited. The high incidence of cirrhosis in tropical countries, associated with infectious diseases peculiar to those regions, is significant. It is admitted that congenital syphilis may result in a form of cirrhosis resembling that bearing the name of Laënnec. Many observers have demonstrated a relationship between streptococcic infection and cirrhosis. It is probable that chronic diffuse infections of the liver are important factors in the etiology of cirrhosis.

It is significant that combinations of agents have been found more effective than either of the same agents alone. The combination of alcohol with phosphorus, of manganese chloride with colon bacilli and of that salt with hydrozine, of chloroform with alcohol, cholesterol, streptococci or colon bacilli, of alcohol with bacteria, and with carbon tetrachloride, and the effects of diet in experiments with phosphorus, chloroform and carbon tetrachloride, are important examples. The results in such instances suggest the importance of combinations of agents in the etiology of human cirrhosis.

A survey of experimental and clinical studies on cirrhosis convinces one that no single causative factor is responsible. Cirrhosis is synonymous with chronic progressive hepatitis. Its etiology will be found to be as variable as are the agents which, singly or in combinations, may cause chronic diffuse progressive inflammation of the liver.

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Notes and News

Inspection of Medical Schools.—H. G. Weiskotten, dean and professor of pathology in the College of Medicine, Syracuse University, has been granted leave of absence for two years to carry on inspection of medical colleges in the United States under the Council of Medical Education and Hospitals of the American Medical Association, the Association of American Medical Colleges and the Federation of State Medical Boards. The work of inspection will begin with the opening of the college sessions for 1934-1935.

Harvard Statement About Patents.—According to *Science*, the Harvard Corporation has issued the following statement: "In the opinion of the Faculties of Medicine, Public Health, Engineering and Arts and Sciences, the patenting by members of the university of discoveries or inventions bearing on matters of health and therapeutics is undesirable. The president and fellows of Harvard College, therefore, have adopted the rule that no patents primarily concerned with therapeutics or public health may be taken out by any member of the university, except with the consent of the president and fellows, nor will such patents be taken out by the university itself unless they be dedicated to the public. The president and fellows will provide legal advice to anyone who desires steps to be taken to prevent the patenting by others of his discoveries or inventions."

Cancer Research at University in Jerusalem.—Some $200,000 has been donated for cancer research at the Hebrew University in Jerusalem. Ludwig Halberstaedter, formerly of the Cancer Institute in Berlin, has been nominated head of the department of radiobiology; H. A. Krebs, formerly of Berlin and now at Cambridge University, England, has been nominated as head of the department of physiologic chemistry, and Leonid Doljansky, formerly of the Institute of Pathology of the University of Berlin and now at the University of Copenhagen, has been nominated as head of the department for the study of cells and tissues and morbid anatomy.

Institute of Legal Medicine in Lille.—A new institute of legal medicine has been opened at Lille, France. Facilities are provided for ordinary medicolegal work as well as for criminal anthropology, penology, occupational diseases and study of delinquents.

Abstracts from Current Literature

Pathologic Anatomy

THE ARTERIAL BLOOD VASCULAR DISTRIBUTION TO THE LEFT AND RIGHT VENTRICLES OF THE HUMAN HEART. LOUIS GROSS and M. A. KUGEL, Am. Heart J. **9**:165, 1933.

By means of a new technic the injection of a standardized barium sulphate gelatin suspension through the coronary arteries has been made possible. Immediately after injection the hearts are fixed in 10 per cent formaldehyde saline solution. After fixation the hearts are cut into transverse slices, 7 mm. thick, and then roentgenograms are made whereby it is possible to study the distribution of the vessels in the myocardium and to compare unit areas in the left and right ventricles. It has been definitely demonstrated that early in life there is a predominance of right ventricular vessels, that there soon follows an equalization of the vascular supply, which lasts for approximately one decade, and that thereafter the vascular bed in the myocardium of the left ventricle assumes an increasing preponderance over that of the right. It has also been shown that the septal anastomoses increase very conspicuously in their extent, particularly after the third decade in life. Both of these observations confirm the earlier report by Gross in this field.

AUTHORS' SUMMARY.

CORONARY OCCLUSION DUE TO METASTASES FROM CARCINOMA OF THE BREAST. T. A. PEPPARD and L. M. LARSON, Am. Heart J. **9**:265, 1933.

Undoubtedly in this case death was caused by an unusual sequence of events which terminated in occlusion of the coronary arteries. Late metastases from an adenocarcinoma of the breast, which had been removed by radical resection five years previously, appeared in a very unexpected location, namely, in the epicardium surrounding the coronary arteries. The mechanism of the localization of the metastases in this particular place is obscure, although unquestionably the blood stream was the medium through which the transfer of malignant cells took place. While in this person a certain amount of arteriosclerotic thickening could be expected because of her age, it probably would have caused few symptoms. However, with the added insult of gradual obstruction of the arterial supply of blood to the heart by the carcinomatous tissue, symptoms and signs of cardiac failure became more and more prominent until death supervened. Metastatic tumors of the heart of various types, while they are comparatively rare, have been reported from time to time, but none has been found which corresponds to the type of lesion described in this case.

AUTHORS' SUMMARY.

XANTHOMATOSIS. KATHARINE K. MERRITT and BERYL H. PAIGE, Am. J. Dis. Child. **46**:1368, 1933.

A case of generalized xanthomatosis (Schüller-Christian's syndrome) with characteristic skeletal changes, exophthalmos, diabetes insipidus and cutaneous lesions is reported. The most unusual feature was the severe cutaneous involvement. Pathologic changes characteristic of the disease were found in the bones, dura mater, hypophysis, infundibulum, periosteum, orbits, skin, thymus, pleura, lungs, heart, peritoneum, spleen, liver, pancreas, lymph glands and retroperitoneal adipose tissue. In the spleen and lymph glands there was extensive hyperplasia of the reticulo-endothelial cells, without evidence of lipoid storage, but in many sites, such as the dura, bones, lungs and thymus, there were typical xanthomatous lesions.

In the skin the corium contained localized accumulations of large mononuclear cells similar morphologically to the reticulo-endothelial cells found in other regions, but in the cutaneous infiltrations few cells contained fat or lipoids.

AUTHORS' SUMMARY.

INTESTINAL LESIONS ASSOCIATED WITH AMEBIC AND BALANTIDIAL INFECTION. H. L. RATCLIFFE, Am. J. Hyg. **19**:68, 1934.

Pathogenic species of Endamoeba and Balantidium have identical effects on the mucosa of the large intestine in susceptible hosts. The primary and perhaps the total effect of the organisms is merely necrosis. They enter the tissue only after necrosis has taken place, except as a postmortem or late antemortem change. The protozoa apparently elaborate a cytotoxic or necrotizing substance that causes tissue degeneration. Lesions are invaded by intestinal bacteria also. Hence extension of tissue necrosis may be due to a combination of factors, and the inflammatory response may not be attributed to the parasites alone. Resistance of the host must be impaired before the intestinal tissues are subject to necrosis. In either balantidiasis or amebiasis, lesions of the intestinal wall originate in the mucous surface. Surface and deep ulcers are genetically the same, except when the latter result from bacterial abscesses of the follicles. The lymphoid tissues of the intestinal wall, because of their anatomic position and make up, are important foci for extension of the disease to the submucosa. Postmortem penetration of tissue by Balantidium and Endamoeba accounts for the fact that isolated organisms and groups of organisms are found deep in the intestinal wall. Balantidium also can invade cut edges of the large intestine at autopsy.

AUTHOR'S SUMMARY AND CONCLUSIONS.

RHEUMATIC PERITONITIS. L. J. RHEA, Am. J. Path. **9**:719, 1933.

Except for the fact that the peritoneal lesions are diffuse rather than focal and sharply outlined, they are similar in every way to the so-called Aschoff bodies found in the heart in this case and in other cases of rheumatic fever. I believe that these lesions are specific, resulting from the action on the peritoneum of the causative agent of the disease. It seems probable that the involvement of the peritoneum in rheumatic fever is more common than is generally thought. If careful microscopic examination is made of tissues from various regions of the peritoneum in instances of rheumatic fever, especially in the severe cases, the specific lesion may be found to be fairly common.

AUTHOR'S CONCLUSIONS.

NODULAR LESIONS OF THE PERITONEUM. S. R. HAYTHORN, Am. J. Path. **9**:725, 1933.

Nearly thirty cases of nodular lesions of the peritoneum which were of interest from the standpoint of surgical diagnosis have been collected, and an outline has been prepared to facilitate the more rapid classification of such lesions.

AUTHOR'S SUMMARY.

THE BONE MARROW IN SPRUE ANEMIA. C. P. RHOADS and W. B. CASTLE, Am. J. Path. **9**:813, 1933.

Observations on the bone marrow in sprue anemia, made on tissue obtained at biopsy in different stages of the disease, show that the changes are similar to those of pernicious anemia. During relapse the essential change is a proliferation of megaloblasts and a suppression of maturation to the normoblast stage. During remission the marrow tends to return to normal with a great increase in the number of normoblasts and mature red cells in the marrow. Phagocytosed erythrocytes were observed in the bone marrow removed at autopsy, but not in that removed during life.

AUTHORS' CONCLUSIONS.

CHANGES IN THE BRAIN DUE TO ARSPHENAMINE. J. H. GLOBUS and S. W. GINSBURG, Arch. Neurol. & Psychiat. **30**:1226, 1933.

A case of syphilis of the brain and one of so-called acute multiple sclerosis were studied. In the former ringlike hemorrhages were present in the optic thalamus, cornu ammonis, tegmentum of the midbrain, pons and cerebellar cortex. In the second case the hemorrhages were scattered in the hemispheres and were especially prominent in the temporal lobes, internal capsule, midbrain and pons; a few were seen in the medulla and spinal cord. In the opinion of the authors, the hemorrhages were capillary and were due to damage of the vascular endothelium.

GEORGE B. HASSIN.

MYOTONIC DYSTROPHY. M. KESCHNER and C. DAVISON, Arch. Neurol. & Psychiat. **30**:1259, 1933.

The histologic changes in a white man, aged 40, in whom the disease lasted eleven years, were: increase in connective tissue in the anterior lobe of the pituitary gland with degeneration of the eosinophilic cells; hyalinization of the interstitial tissue of the thyroid gland; central fibrosis of the parathyroid glands; fibrosis of the fascicular layer of the suprarenal glands, and atrophy of the seminiferous tubules of the testes with increase in Leydig's cells. The muscles, smooth and striated, had an increase in the sarcolemmic nuclei with loss of striations and hyalinization in many instances. In the brain, a spongioblastoma of the corpus callosum, the size of a pea, was found which had given no clinical symptoms. The ganglion cells of the hypothalamic and paraventricular nuclei and of the lateral columns of the spinal cord showed marked chromatolysis, tumefaction and disintegration, while the thalamus and the nuclei of the medulla presented milder changes. In the sister of this patient who also suffered from myotonic dystrophy a biopsy revealed a proliferation of connective tissue in the muscles, which were replaced by fat and chains of sarcolemmic nuclei. The primary changes are not in the sympathetic nervous system, but in the muscles; the changes in the lateral horn cells are secondary.

GEORGE B. HASSIN.

PATHOGENESIS OF APOPLECTIC CEREBRAL HEMORRHAGE. T. VON LEHOCZKY, Beitr. z. path. Anat. u. z. allg. Path. **92**:132, 1933.

To determine whether apoplectic cerebral hemorrhage is the result primarily of vascular disease, as is generally believed, or of disease of the cerebral parenchyma, as some recent observers maintain, von Lehoczky examined histologically the brains of fourteen persons who died of such hemorrhage. When death occurred within a few hours after the hemorrhage, there were observed fibrillar separation and marked hypertrophy of the glia in and about the area of hemorrhage. He believes that this parenchymatous lesion was present before the hemorrhage occurred and was a factor in it. Vascular disease was present in all the brains. He concludes that cerebral hemorrhage may be due to disease of the parenchyma, to vascular disease or to arterial hypertension, the three factors often operating together.

O. T. SCHULTZ.

ABLATION OF THE PLEURA AND RUPTURE OF PULMONARY TISSUE. F. ORSÓS, Beitr. z. path. Anat. u. z. allg. Path. **92**:173, 1933.

Orsós reports nine examples of ablation of the pleura or rupture of pulmonary tissue. The cases represent a variety of clinical conditions, but in all there was round cell infiltration of the lung or pleura. The tearing of the inflamed and weakened tissue was a terminal event and was the result of dyspnea or violent respiratory efforts. The air-filled spaces formed beneath the pleura or in the lung are not to be confused with those seen in emphysema.

O. T. SCHULTZ.

PECULIAR MALFORMATION OF THE PULMONARY VEINS. H. REBENSBURG, Frankfurt. Ztschr. f. Path. **44**:137, 1932.

A male infant died suddenly about three months after birth. The left ventricle was much smaller than the right. The aorta showed no changes, and the ductus arteriosus was obliterated. There was no communication between the left auricle and the lungs, the pulmonary veins not being in their normal location. The foramen ovale was wide open and round, measuring 5 mm. in diameter, and the right auricle was three times as large as the left. Into the right auricle opened the coronary veins and the superior and inferior venae cavae, in addition to another vein which extended from the right upper lobe of the lung into the auricle. Another pulmonary vein took its course from the lower lobe of the right lung to the lower lobe of the left lung, forming a bridge between these lobes. This vein also extended throughout the entire left lung to the region of the hilus, collecting smaller tributaries, and opened into the superior vena cava just above the right auricle. The pulmonary arteries were normal. The arterial blood took the following courses from the lung to the heart; from the right upper lobe into the right auricle; from the right lower lobe to the left lung and from there to the superior vena cava and also into the right auricle; from the right auricle through the patent foramen ovale into the left auricle.

O. SAPHIR.

SO-CALLED SEPTIC INFLAMMATION OF THE SPLEEN. K. VON WOLFF, Frankfurt. Ztschr. f. Path. **44**:161, 1932.

By injecting foreign proteins (milk), Wolff attempted to produce changes in the spleen similar to those seen in cases of sepsis. The conclusion is reached that so-called septic inflammation of the spleen is not the direct result of the presence of micro-organisms but is caused by protein material set free by destruction of cells. Therefore, the terms toxic splenitis, septic splenitis, and the like are incorrect; "splenitis albuminotoxica" seems more significant.

O. SAPHIR.

TWO CASES OF AGRANULOCYTOSIS IN CHILDREN. R. GANSER, Frankfurt. Ztschr. f. Path. **44**:329, 1932.

The important manifestations in these cases were hemorrhagic diathesis, enlargement of the liver and mastoiditis. Angina was present in one case. In both instances the blood showed marked reduction in the number of the red corpuscles and marked leukopenia, with relative lymphocytosis and thrombopenia. In addition, the second case revealed polychromatophilia of the red corpuscles and a moderate number of normoblasts. Several blood transfusions were given, resulting in an improvement of the blood picture. Gradually, however, the anemia and leukopenia recurred. Autopsy revealed hemorrhages into the skin, the serous and mucous membranes, the myocardium, the surface of the liver and kidneys and the subperiosteal space. In the first instance the lymph nodes in the region of the neck and hilus of the liver were moderately enlarged, while in the second case all the lymph nodes were enlarged. The mucosa covering the tonsils showed areas of hemorrhage and necrosis. The bone marrow of the femur was dark red in both instances. Histologic examination of the bone marrow revealed an almost complete disappearance of granulocytes and megakaryocytes. Erythrocytes, erythroblasts and a large number of cells that showed only a small amount of cytoplasm were present. The nuclei of the latter varied in size. These cells resembled microlymphocytes and mesolymphocytes. Also, cells apparently identical with the hemocytoblast (stem cell) of Maximow were recognized. The lymph nodes revealed microlymphocytes, mesolymphocytes and a few macrolymphocytes and hemocytoblasts. Occasionally eosinophilic myelocytes were also seen. The spleen contained microlymphocytes and mesolymphocytes, a few plasma cells, myelocytes and many partially destroyed erythrocytes. Small and large lymphocytes were present in the liver in addition to eosinophilic myelocytes, which were

abundant in the second case. In spite of the presence of many microlymphocytes and mesolymphocytes, Ganser does not believe that these two cases are characteristic of chronic (aleukemic) lymphadenosis. He believes that these cells are closely related to the hemocytoblasts and very likely are myeloid cells. It is possible that the stem cells and their derivatives are increased in number because of a pathologic irritation. Ganser concludes that severe damage, possibly combined with a constitutional factor, produces marked destruction and necrosis of the bone marrow and may be responsible for the picture of so-called panmyelophthisis. A less severe irritation may produce atrophy of the blood-forming organs. Another type of irritation, still less severe, may cause, in addition to atrophy, regenerative and compensatory blood formations in the bone marrow and other organs. He believes that the latter explanation holds for the two cases reported.

O. SAPHIR.

HISTOLOGIC CHANGES OF THE LYMPH NODES IN CASES OF LYMPHOGRANULOMATOSIS (HODGKIN'S DISEASE). H. HAMDI and SAIM-ALI, Frankfurt. Ztschr. f. Path. **44**:338, 1932.

The lymph nodes of six persons showing Hodgkin's disease were examined. The small nodes revealed a marked increase in the number of lymphocytes and occasionally in the numbers of eosinophilic and plasma cells. These changes are thought to be the initial stages of Hodgkin's disease. In the enlarged lymph nodes were found a number of epithelioid cells, varying numbers of lymphocytes, polymorphonuclear neutrophilic and eosinophilic cells, plasma cells and giant cells, areas of hyalinization and connective tissue fibers. In addition, foci of necrosis were seen. The epithelioid cells were round, oval or sometimes polygonal. Their cytoplasm was abundant and occasionally revealed pseudopodia-like elongations. The nuclei were large, round and often lobulated. They were distinctly vesicular, revealed a fine chromatin network and granules, and contained one or two metachromatic nucleoli. Mitotic figures were present. Some of these cells were unusually large and revealed several nuclei. Cells of the latter type probably originated from the perithelial cells of blood vessels. It is also possible that they arose from the reticulo-endothelial system. It is likely that the giant cells resulted from the confluence of several epithelioid cells. In the larger and older nodes the strands of connective tissue extended from the capsule into the granulation tissue. The various stains for the presence of bacteria did not reveal uniform results. Occasionally, organisms of the Corynebacterium group could be demonstrated by the use of Gram's method. Fresh portions of lymph nodes transplanted into rabbits and mice grew in only one instance. The transplant contained bacteria and connective tissue fibers but showed no granulomatous changes.

O. SAPHIR.

FREQUENCY AND ORIGIN OF SO-CALLED ROUND CELL FOCI IN THE SUPRARENAL GLANDS. A. COSTA, Frankfurt. Ztschr. f. Path. **44**:343, 1932.

Foci of round cells are found in the human suprarenal glands at every age. In children similar cells are isolated and in very small groups; they are more common in the zona reticularis. Later they extend into the zona fasciculata.

O. SAPHIR.

INCOMPLETELY FORMED CORPUS CALLOSUM REPLACED BY FATTY TISSUE. B. G. RUBINSTEIN, Frankfurt. Ztschr. f. Path. **44**:379, 1932.

A series of anomalies were found in the brain of a 30 year old man who had had epileptic attacks since childhood. The corpus callosum was partly absent. There was hypoplasia of the middle portion of the fornix, of the choroid plexus and of the third ventricle. The septum pellucidum and the lyra were absent, and the columnae fornicis revealed an abnormal course. In place of the corpus

callosum fatty tissue was found, which is explained as a secondary process. Since fat was also present in the choroid plexus, the fat probably extended from there into the region of the corpus callosum.

O. SAPHIR.

DELAYED THORIUM DIOXIDE NECROSIS OF LYMPH NODES. T. NAEGELI and A. LAUCHE, Klin. Wchnschr. **12**:1730, 1933.

During three years' observation of a dog given intravenous injections of thorium dioxide there was no appreciable excretion of this compound. The dioxide was transported from the site of initial deposition into the regional lymph nodes, where it produced extensive necrosis. The further fate of the thorium dioxide is speculative. Probably some became encapsulated and some was carried into other lymph nodes.

AUTHOR'S SUMMARY.

PENETRATION OF A GASTRIC ULCER INTO THE WALL OF THE HEART. W. EHRHARDT, Virchows Arch. f. path. Anat. **289**:327, 1933.

A woman, aged 63, who had been ill for two months with symptoms referable to an inoperable carcinoma of the sigmoid flexure died suddenly of heart failure. Necropsy revealed, in addition to the carcinoma, an ulcer of the lesser curvature of the stomach that had penetrated the diaphragm and eroded the outer portion of the wall of the left ventricle. The heart was adherent to the pericardium only in this region. The ventricular wall was not perforated. Seven previously reported cases of this unusual complication of gastric ulcer are discussed.

O. T. SCHULTZ.

SUBAORTIC DEFECT OF THE INTERVENTRICULAR SEPTUM OF THE HEART. H. TESSERAUX, Virchows Arch. f. path. Anat. **289**:412, 1933.

The heart described was that of a boy, aged 12 years, who died of acute leukemia. The heart was enlarged to about three times its normal size. In the anterior upper part of the interventricular septum was an opening that measured 11 by 17 mm. on the side of the left ventricle, where it was situated below the right and left segments of the aortic valve. On the right side the opening was smaller and was at a considerable distance from the ostium of the pulmonic artery. The defect was situated above the conduction system. The few previously reported instances of a defect in this unusual situation are reviewed by the author. He ascribes the defect to an abnormally large embryonic interventricular foramen.

O. T. SCHULTZ.

SOME UNUSUAL MALFORMATIONS. F. GRÖGLER, Virchows Arch. f. path. Anat. **289**:430, 1933.

Four fetuses with craniorachischisis, two acardiac monstrosities and one phocomelus with the defect limited to one upper extremity are described. Craniorachischisis is ascribed by Grögler to the action of external factors. The phocomelus was a woman who died at the age of 21 of pulmonary tuberculosis. The forearm, two phalanges and part of the carpus were absent.

O. T. SCHULTZ.

Microbiology and Parasitology

PRENATAL TRICHINOSIS. D. L. AUGUSTINE, Am. J. Hyg. **19**:115, 1934.

Observations on rabbits, rats, swine and a child born of trichinous mothers confirm the conclusion of Stäubli (1909) that prenatal infection does not occur in trichinosis.

AUTHOR'S CONCLUSION.

THE SELF-DISINFECTING POWER OF THE SKIN. L. ARNOLD and A. BART, Am. J. Hyg. **19**:217, 1934.

Living bacteria placed on the skin rapidly disappear. They cannot be demonstrated by cultural or tinctorial methods thirty or forty minutes after contact with the skin. Attempts have been made to determine the presence of antigenic substances placed on the skin. Bacillus enteritidis and fresh egg-white placed on cutaneous surfaces and allowed to dry in the air could not be demonstrated in washings collected from such exposed surfaces. These antigens could be demonstrated in cornified epithelial scrapings mechanically removed from such exposed skin. The human skin possesses a power of destroying exogenous bacteria placed in contact with it. Desiccation is not a major factor in this mechanism of controlling the viable bacterial flora on a clean cutaneous surface. Evidence is presented to indicate that keratin may play a rôle in the removal of bacterial as well as other antigens from human skin.

AUTHORS' SUMMARY.

THE CLINICAL SIGNIFICANCE OF B. COLI HEMOLYTICUS. WALTER L. NILES and JOHN C. TORREY, Am. J. M. Sc. **187**:30, 1934.

Strains of the colon bacillus possessing hemolytic properties are frequently isolated from human feces (31 to 45 per cent of stools). They are somewhat more often found and in larger numbers in feces from patients with disorders relating to the digestive tract. There is no distinctive difference as regards morphology or cultural characteristics in the hemolytic strains of the colon bacillus isolated from the stools of normal and sick people, although those from the former group have seldom exhibited any virulence. We have been successful in relieving the symptoms of toxemia by autogenous vaccines. Bacillus coli-haemolyticus has thus been eliminated from the feces in 93 per cent of our cases. It has reappeared in 3 per cent after one year or longer. Vaccination is the only method for eliminating B. coli-haemolyticus from the human feces which we have found effective.

AUTHORS' SUMMARY.

CONJUGAL SYPHILIS—A STATISTICAL STUDY. HENRY B. DECKER, Am. J. M. Sc. **187**:111, 1934.

There is presented an investigation of the records of 376 families in which syphilis was present in at least one spouse; 60 husbands and 98 wives were syphilitic with nonsyphilitic spouses. In 218 families both husband and wife were syphilitic. It is concluded that the type of syphilis depends on the individual rather than on any special strain of spirochetes. Late syphilis is relatively noninfectious. Infectivity varies inversely with the duration of the disease.

AUTHOR'S SUMMARY.

THE ETIOLOGY OF MUMPS. C. D. JOHNSON and E. W. GOODPASTURE, J. Exper. Med. **59**:1, 1934.

From four of six specimens of saliva taken in six cases of mumps in the early stages of the disease a filtrable cytotropic virus has been obtained which induces in rhesus monkeys, following its injection into the parotid gland through Stensen's duct, an acute nonsuppurative parotitis analogous to mumps. This virus has not been found in normal saliva, nor does it correspond to any known virus with which we are familiar. The virus is free from demonstrable micro-organisms including spirochetes. It is judged that this virus is the causative agent in mumps.

AUTHORS' CONCLUSIONS.

THE SIGNIFICANCE OF HORMONAL FACTORS IN EXPERIMENTAL POLIOMYELITIS. C. W. JUNGEBLUT and E. T. ENGLE, J. Exper. Med. **59**:43, 1934.

Adult rhesus monkeys possess frequently a greater resistance to experimental infection with the virus of poliomyelitis than young monkeys, as indicated by the prolongation of the incubation period and by the content of feeble neutralizing substances in the normal serum. Virucidal substances can be demonstrated in the normal serum of subadult chimpanzees. Immature monkeys prepared with anterior lobe pituitary hormones and the like principles from the urine of pregnant women are only in exceptional instances protected against intracerebral infection with poliomyelitic virus. However, the serum of such prepared animals frequently acquires the property of inactivating the virus in vitro. Active immunization with the live virus renders the immunized monkeys resistant to intracerebral infection in a higher percentage of the cases than does preparation with hormones. The relative merits of nonspecific enhancement of resistance and of specifically acquired immunity are discussed in their relation to the probable mechanism of resistance to poliomyelitis in man.

AUTHORS' CONCLUSIONS.

SIMILARITIES BETWEEN EXPERIMENTAL SCURVY COMBINED WITH INFECTION AND RHEUMATIC FEVER. J. F. RINEHART, C. L. CONNOR and S. R. METTIER, J. Exper. Med. **59**:97, 1934.

In the guinea-pig, chronic scurvy with superimposed infection (beta hemolytic streptococcus), and to a lesser extent chronic scurvy alone, produces an arthropathy with striking pathologic similarities to that of rheumatic fever and the closely allied condition of rheumatoid arthritis. Considerable significance is attached to the widespread occurrence in the animal subjected to scurvy and infection, and to a lesser extent in scurvy alone, of lesions similar to if not identical with the fibrinoid degeneration which has been considered the fundamental lesion of rheumatic fever. A subcutaneous nodule essentially similar to the subcutaneous nodules of rheumatic fever was observed in one experimental animal. Attention is called to a group of general pathologic changes frequently observed in rheumatic fever which were also found in the animals subjected to scurvy and infection. These include degenerative changes in skeletal muscle, focal necrosis in the liver, fibrosis of the malpighian bodies in the spleen, erythrophagocytosis in the lymph nodes and focal lymphocytic accumulations in the kidneys. The problem of hemorrhage is considered. It is suggested that a scorbutic state may be the basis of the hemorrhagic manifestations common to the acute phases of rheumatic fever. The unsatisfactory nature of previous attempts to reproduce rheumatic fever is noted. The lesions produced by subjecting the guinea-pig to the combined influence of scurvy and infection are considered to be fundamentally similar in character and distribution to those of rheumatic fever. The observations recorded are believed to offer evidence that the disease known as rheumatic fever may be the result of the combined influence of scurvy and infection, and that scurvy may constitute the rheumatic tendency in which the added factor of infection causes the development of rheumatic fever or possibly the closely allied condition of rheumatoid arthritis.

ACUTE ASCENDING MYELITIS FOLLOWING A MONKEY'S BITE. A. B. SABIN and A. M. WRIGHT, J. Exper. Med. **59**:115, 1934.

A case of acute ascending myelitis which followed the bite of an apparently normal rhesus monkey is described. The absence of perivascular demyelinization removes the case from the realm of acute disseminated encephalomyelitis and establishes it more or less definitely as one of primary acute infectious myelitis. An extremely important pathologic feature was the focal necrosis in the spleen, suprarenal glands and regional lymph nodes. Attempts to transmit the disease to rhesus monkeys, dogs, mice and guinea-pigs, employing glycerinated organs from the patient, proved unsuccessful. By inoculations of rabbits the presence of a strongly neurotropic filtrable virus was demonstrated in the patient's brain, cord

and spleen. Following intracutaneous injection of the virus as derived either from brain and cord or from spleen, an experimental disease developed in rabbits which strikingly resembled the human disease in the character of the local lesion, the period of incubation, the development of urinary retention, the flaccid paralysis of the posterior extremities with cephalad progression, the death by respiratory failure, and finally the observation of focal necrosis in the spleen, suprarenal glands and liver. In attempting to establish the identity of this virus (the B virus), a considerateion of its biologic properties excludes the viruses of poliomyelitis, rabies, vaccinia and virus III disease of rabbits and the other viruses which are known to produce similar intranuclear inclusions, except perhaps that of herpes. Although the relationship between the B virus and the virus of herpes must still be determined by cross-immunity tests the B virus has been shown to possess certain properties which warrant consideration of it as a distinct entity.

From the Authors' Summary.

The Conversion of Typhus Strains. H. Mooser and others, J. Exper. Med. **59**:137, 1934.

It is concluded from our experiments that there does not exist any real difference between the virus of historic Old World typhus and the murine New World typhus. Both are considered to be of murine origin. The murine strains represent the original form of the virus of typhus, whereas the epidemic strains are the result of a prolonged propagation in the cycle man-louse-man.

From Authors' Summary and Conclusions.

The Viruses of Vesicular Stomatitis and Equine Encephalomyelitis. P. K. Olitsky and others, J. Exper. Med. **59**:159, 1934.

The viruses are similar in many biologic properties. In view of the fact that the horse is the natural host for both it is suggested that they may be generically related. They are not, of course, identical, since cross-immunity does not exist. This, however, does not exclude the possibility of a generic relationship, for there are at least three immunologically distinct types of foot and mouth diseases, two of vesicular stomatitis, and two of equine encephalomyelitis.

From Authors' Summary.

The Survival of Neurotropic Yellow Fever Virus in Testicular Tissues. W. Lloyd and A. F. Mahaffy, J. Immunol. **25**:471, 1933.

Neurotropic yellow fever virus of the French strain and of mouse origin has been transferred through nine passages in the testicular tissues of albino mice. Virus isolated from the sixth and seventh passages in the testes of mice has been demonstrated to give a specific immunologic reaction as yellow fever virus in passive immunity tests. Testicular virus of mouse origin when injected subcutaneously into a rhesus monkey resulted in the immunization of the animal, with the development of only a retarded and mild febrile reaction.

Authors' Summary.

The Infectivity of Neurotropic Yellow Fever Virus for Animals. G. M. Findlay, J. Path. & Bact. **38**:1, 1934.

After intracerebral inoculation neurotropic yellow fever virus produces an encephalitis not only in mice and guinea-pigs but also in field voles and red squirrels. Cats, ferrets, rabbits, rats, golden hamsters, wood voles, bank voles, pigeons, hens and canaries are not susceptible and suffer neither encephalitic changes nor viscerotropic lesions. Little or no multiplication occurs in the brain of a nonsusceptible species such as the rat. The neurotropic virus is capable of surviving for a few days in the brains of nonsusceptible species. Immune bodies for neutro-

tropic yellow fever virus are not present in the blood of nonsusceptible species before inoculation, but may subsequently appear in the blood.

AUTHOR'S CONCLUSIONS.

GENERALIZED VACCINIA IN MAN. J. H. DIBLE and H. H. GLEAVE, J. Path. & Bact. **38**:29, 1934.

A study has been made of the lesions in a case of generalized vaccinia in a child aged 3 months who died on the twenty-sixth day after vaccination. The skin pocks appeared clearly as primary epithelial necrosis without any granulomatous changes in the corium. The visceral lesions, like the epidermal, were purely necrotic without hemorrhage and with only a minimum reactive change. There were no vaccinial lesions found in the lungs, the brain or the suprarenal glands.

FUNGI FROM BLASTOMYCOSIS. A. CASTELLANI and I. JACONO, J. Trop. Med. **36**:297, 1933.

Blastomycosis may be caused by many different fungi. Cultures of the fungi described in the paper will be supplied to interested workers by the authors (Ross Institute and Hospital for Tropical Diseases, London).

EXPERIMENTAL SYPHILIS IN LABORATORY ANIMALS. J. VAN HAELST, Arch. internat. de méd. expér. **8**:543, 1933.

Syphilis ran a typical course in rabbits and guinea-pigs regardless of the quantities of spirochetes in the inoculated material. Evidences of syphilis became apparent more quickly if syphilitic lymph nodes were employed for inoculation than if syphilitic testis was used. In either case the period of incubation lengthened as the infective material was diluted. In the rabbit the potential infectiveness of syphilitic testis was greater than that of syphilitic inguinal or popliteal nodes, in the sense that testis was capable of provoking a primary lesion when used in a dilution ineffective in the case of the nodes. A striking difference in minimum infective dosages of these tissues could not be explained on the basis of the relative numbers of spirochetes contained. Syphilitic guinea-pig lymph node was peculiar in that it was much more infective than syphilitic rabbit testis. In the guinea-pig, more manifestly than in the rabbit, the period of incubation of the primary lesion was longer than usual if infected node, rather than testicle, was inoculated. Large doses of syphilitic material appeared to shorten the period of incubation, but minimum doses showed no tendency to lengthen it. Spirochetes were detected in 95.65 per cent of syphilitic rabbit nodes examined. Nodes draining active lesions were found to contain greater numbers of spirochetes than nodes from the region of healed lesions. Great numbers of spirochetes were found in the regional lymph nodes on the day following inoculation. In the clinically nonapparent syphilis of the mouse, spirochetes were seen not only in the superficial nodes but also in the spleen and brain. Spirochetes were most numerous in the lymphoid tissues of the mouse. In the rabbit, the minimum infective dose bore a direct relation to the quantities of spirochetes contained when tissues relatively poor in spirochetes were employed. The minimum infective dose of lymph node, a tissue poor in spirochete content, approached a constant value which was less than that required when other tissues containing many more spirochetes were employed. In infecting the rabbit with syphilis by inoculation of guinea-pig and mouse tissues, the factors of actual spirochete content and of specific infectivity of tissues poor in spirochetes seemed equally important in influencing the length of incubation of the primary lesions. Finally, it seemed that the presence of spirochetes was enough to explain the specific infectiveness of tissues which were low in actual spirochete content. Taken individually, spirochetes present in the primary lesion were probably less virulent than those in the regional nodes. The nodes apparently served to adapt the spirochete to live in the host, so that there was a rise in virulence.

FROM AUTHOR'S SUMMARY.

DETERMINATION OF TUBERCLE BACILLEMIA IN CHILDREN. JOSEPH SIEGL, Beitr. z. Klin. d. Tuberk. **81**:557, 1932.

Siegl sent equal parts of identical blood specimens to Dr. Loewenstein and Dr. Maresch for cultivation of tubercle bacilli by Loewenstein's method. A third aliquot portion was sedimented and injected into guinea-pigs. The specimens were obtained from 140 children; some of these had active tuberculosis, others reacted positively to tuberculin but had clinically inactive tuberculosis, and the remainder gave negative reactions to tuberculin. Dr. Loewenstein's laboratory reported 13.5 per cent positive cultures for those with active tuberculosis, 18.9 per cent positive results for those with inactive tuberculosis, and 23.9 per cent positive findings for those with negative tuberculin tests. Dr. Maresch's laboratory reported that 5.1 per cent of the specimens contained tubercle bacilli, and these specimens were all from children with active tuberculosis. Moreover, only once did both these experimenters isolate tubercle bacilli from the same person's blood. Also only one guinea-pig presented tuberculosis following inoculation and that from a specimen which both laboratories had reported as negative. Siegl also distributed urine, sputum and pus containing tubercle bacilli to the same two laboratories, and although many positive results were reported, in only three specimens did both laboratories report identical results. Of the eleven positive cultures that Loewenstein reported for children who gave negative reactions to tuberculin, six produced typical tuberculosis in guinea-pigs. Siegl concludes that it is not as yet possible to resolve these contradictions.

AARON EDWIN MARGULIS.

BRONCHIOGENIC TUBERCULOSIS IN CHILDREN. L. DE VELASCO, Beitr. z. Klin. d. Tuberk. **81**:674, 1932.

The author investigated the significance of bronchiogenic propagation in the development of pulmonary tuberculosis in childhood. The material consisted of thirty-two children, aged from 9 months to 6 years, who came to autopsy. Thirteen showed undoubted evidence of extension by the bronchiogenic route. In general, these bronchiogenic foci showed the same differentiation into those due to small seedings and those due to coarse seedings as Loeschcke has described in adults. In eight cases the source of the propagation was excavation of a primary focus, while in six cases a caseated lymph node had ruptured into a bronchus. In the absence of evidences of hematogenous dissemination, however, caseation of lymph nodes was slight, and intranodular hemorrhagic foci were absent. This likewise parallels the histologic picture of the disease in adults.

AARON EDWIN MARGULIS.

THE INFLUENCE OF ALTITUDE ON TUBERCULOSIS IN GUINEA-PIGS. LUDWIG LANGE and OTHERS, Beitr. z. klin. d. Tuberk. **82**:1, 1933.

Extensive, identical experiments were conducted simultaneously at four altitudes (sea level, 375 meters, 1,570 meters and 3,100 meters). At each station the animals were divided into two groups, one of which was kept in the dark and the other in diffuse daylight. In addition, a portion of the latter were sensitized to light with eosin. Some of the guinea-pigs were allowed to become acclimated to the altitude before the start of the experiments, and others were inoculated immediately on arrival at the respective stations. All were given injections of similar amounts of identical strains of tubercle bacilli. Records were kept of duration of life and changes in weight, and on autopsy studies were made of the histologic aspects and distribution of the disease. The only significant findings were that the lowest death rate occurred in the nonsensitized animals kept in the light, and the highest death rate in the eosin-sensitized animals kept in the light at high altitudes. No other significant deviations as between the different stations were noted.

AARON EDWIN MARGULIS.

THE GENESIS OF ACUTE, GENERAL, MILIARY TUBERCULOSIS. I. MINGUEZ, Beitr. z. Klin. d. Tuberk. **82**:84, 1933.

This study is based on thirty-nine autopsies. In each Minguez searched for the focus of the spread, using as criteria Loeschcke's postulates: liquefaction of contents, presence of a large number of bacilli and presence of blood as an indication of rupture into a blood vessel. He believes that endovascular tubercles are the result and not the cause of bacillemia. In thirty-one cases such foci were certainly demonstrated, and in eight doubtfully so. The focus was in a lymph node in twenty-two instances; it was primary three times; it was in a caseated testicle once, and in the remaining three cases it was indeterminate.

AARON EDWIN MARGULIS.

EXPERIMENTAL TUBERCULOSIS OF THE BONES. M. MANDELSTAMM, Beitr. z. Klin. d. Tuberk. **82**:98, 1933.

Rabbits were inoculated with bovine tubercle bacilli intra-articularly, intracardially and subcutaneously. Metastatic tubercles appeared in all elements of the bony system except the fat marrow. In general, they were distributed perivascularly, the arteries themselves, however, never showing any tuberculous infiltrations. The tubercles that appeared in the myelogenous bone marrow of the diaphyses did not caseate, while those which appeared in the metaphyses developed more rapidly and frequently caseated. Thus clinical experimental bone tuberculosis in the rabbit, as in the human being, starts in the epiphyseal region. This is interpreted as evidence of significant variation in local resistance of specific tissue.

AARON EDWIN MARGULIS.

NEW BLOOD VESSEL FORMATION IN PULMONARY TUBERCULOSIS AND ITS SIGNIFICANCE FOR TUBERCLE BACILLEMIA. JOSÉ ABÉLLO PASCUAL, Beitr. z. Klin. d. Tuberk. **82**:152, 1933.

Studying sections stained with hematoxylin alum and acid fuchsin, Pascual demonstrated that the new-formed capillaries in richly vascularized tuberculous granulation tissues frequently contain either phagocytosed or free tubercle bacilli. This manner of invading the blood, although not the only one, may have major significance in the development of tuberculosis.

AARON EDWIN MARGULIS.

SERUM LIPASE CHANGES IN EXPERIMENTAL TUBERCULOSIS. J. BALÓ, F. GERLEI and L. LOVAS, Beitr. z. Klin. d. Tuberk. **82**:164, 1933.

Forty rabbits were inoculated with bovine tubercle bacilli. Half received, in addition, intravenous injections of pancreatic extract, at first daily and subsequently at longer intervals. The controls uniformly showed a decrease in serum lipase, while those receiving the pancreatic extract showed either no significant variations or, as happened in most instances, a distinct rise in the serum lipase.

AARON EDWIN MARGULIS.

TOXIC GRANULATIONS IN LEUKOCYTES IN TUBERCULOSIS. J. LEITNER and W. EICHORN, Beitr. z. Klin. d. Tuberk. **82**:173, 1933.

The authors discuss the significance of toxic granulations in leukocytes. As regards tuberculosis, although the granulations occur most often in the presence of exudative processes, in which sometimes all the polymorphonuclear cells show such granulations, they also occur when the processes are productive. Hence, although they tend to occur in greater number in severe cases, their diagnostic and prognostic value is limited. However, taken in connection with a Schilling or Arneth count, their presence is worthy of consideration.

AARON EDWIN MARGULIS.

TYPHOID BACILLUS MENINGITIS. J. WEEBER, Beitr. z. path. Anat. u. z. allg. Path. **92**:223, 1933.

In the Szent-László Hospital of Budapest, Hungary, there were in the years 1922 to 1932, inclusive, 10,327 necropsies. This number included 1,131 cases of typhoid, one of which was complicated by meningitis due to the typhoid bacillus. In this case relapse occurred in the eighth week, and meningeal symptoms developed in the twelfth week, death occurring on the tenth day after the onset of meningeal symptoms. Typhoid bacilli were cultivated from the purulent spinal fluid withdrawn during life. Histologically the process was characterized by a predominance of lymphocytes and by the presence of many large phagocytic cells.

O. T. SCHULTZ.

YELLOW FEVER VIRUS IN TISSUE CULTURE WITH ESPECIAL REFERENCE TO ITS CULTIVATABILITY. E. HAAGEN and M. THEILER, Zentralbl. f. Bakt. (Abt. 1) **125**:145, 1932.

The virus of yellow fever (French strain) behaves in tissue cultures in general like the viruses of variola, vaccinia, herpes and foot and mouth disease. By Theiler's method of intracerebral injection into mice it was found that the virus requires living cells for its maintenance in vitro; in the absence of living cells or on the addition of killed cells the virulence is soon lost. The virulence in numerous passages remained constant, and the authors therefore conclude that the cultivation of the virus was achieved.

PAUL R. CANNON.

THE SIGNIFICANCE OF BACTERIUM GRANULOSIS (NOGUCHI) IN TRACHOMA. C. J. SCHUURMAN, Zentralbl. f. Bakt. (Abt. 1) **125**:158, 1932.

Schuurman made a search for Bact. granulosis in 33 patients with trachoma, using the technic given by Noguchi. Seventy-three strains of bacteria were isolated, none of which was identical with either of two strains of Bact. granulosis obtained from America. He concludes that this organism is of no significance in the etiology of trachoma in Java, and suggests that more attention should be paid to the cell inclusions described by Prowazek.

PAUL R. CANNON.

EXPERIMENTAL SYPHILIS OF THE CENTRAL NERVOUS SYSTEM OF RABBITS. T. TANI and K. SAITO, Zentralbl. f. Bakt. (Abt. 1) **125**:417, 1932.

Syphilitic testicular emulsions containing spirochete strain "VIII" were injected into the brains of rabbits to determine the optimum method for obtaining infection, as revealed by the development of a positive Wassermann reaction in the spinal fluid. The best results were obtained in full-grown male albino rabbits receiving injections into the parietal lobes or into the subarachnoidal space with 0.5 cc. of the emulsion, given four times at intervals of one week. Of the sixty-four rabbits given injections, forty-eight lived more than thirty days, and forty-six of these gave a positive Wassermann reaction of the spinal fluid.

PAUL R. CANNON.

Immunology

THE TOXIC PROPERTIES OF SERUM EXTRACTS OF HEMOLYTIC STREPTOCOCCI. J. T. WELD, J. Exper. Med. **59**:83, 1934.

A method is described whereby toxic substances may be extracted from hemolytic streptococci with inactivated serum. Such extracts contain large amounts of hemotoxin and leukocidin. Their intravenous injection into mice causes marked hemoglobinuria, anemia and death. There is evidence that the anemia is not the only cause of death. Incomplete work seems to indicate that the hemotoxin and the lethal poisons are not antigenic. Certain biologic properties of the extract are described.

AUTHOR'S CONCLUSIONS.

TISSUE REACTIONS IN IMMUNITY. REUBEN L. KAHN, J. Immunol. **25**:295, 307, 317, 331, 339, 347 and 363, 1933.

The report consists of seven articles. The skin tests for the estimation of the sensitivity of rabbits were done by injecting intradermally 0.1 cc. of increasing dilutions of the antigen. The highest dilution producing an inflammatory reaction after twenty-four hours gave the titer of skin sensitivity. A symbolic formula was employed to express quantitatively the extent and intensity of the inflammatory response (for instance, $4R_8$ In_8, $3B_8$ means that the response was a markedly raised [edematous] red area, 4 cm. in diameter with a central black necrotic area 3 cm. in diameter). The titer of precipitins in the serum was determined by mixing 0.1 cc. quantities of dilutions of the antigen with similar quantities of the serum. The tests were read on the following day. There was some correlation between the titers of skin sensitivity and those of the serum precipitins during the first weeks following sensitization; later the precipitins in the serum tended to decrease and eventually to disappear, while the cutaneous sensitivity persisted. Tissue hypersensitiveness is a more permanent response than precipitin production, and the two phenomena are independent of one another. Desensitization of rabbits sensitized with human serum was accomplished by intravenous injections of 5 cc. of the serum per kilogram of body weight in one series and 0.5 cc. per kilogram of body weight in another series of four animals with low precipitins or absence of precipitins. The skin sensitivity and the precipitins disappeared following the intravenous injection. They returned gradually after forty-eight hours, the precipitins coming back more rapidly. Desensitization was also successful in rabbits sensitized to egg-white and to horse serum. Heretofore, desensitization was considered possible only in the case of a simple protein in crystalline form. A marked increase in the intensity of the cutaneous inflammatory reactions remaining from previous skin tests was noted following the desensitizing injections. In rabbits receiving desensitizing intravenous injections of bacterial suspensions, necrotic lesions appeared rapidly even in areas where before the intravenous injection no local response was noticeable after intracutaneous injections of the antigen. Intravenous injections of typhoid and paratyphoid A bacilli into immunized rabbits (4 cc. per kilogram of body weight of bacterial suspensions containing 3 billion organisms per cubic centimeter) succeeded in marked, though only temporary, reductions of cutaneous sensitivity, without affecting the titer of agglutinins. Similar injections of typhoid, paratyphoid A and colon bacilli and hemolytic streptococci into normal, not artificially sensitized rabbits removed temporarily their normal cutaneous senstivity to these micro-organisms and led to a similar increase of intensity of the local inflammatory reactions which remained after tests for cutaneous sensitivity. The results of Schultz and Swift were confirmed concerning the development of a more marked skin sensitivity in rabbits given intradermal injections of hemolytic streptococci, while intravenous injections stimulated mainly a rise of the agglutinin and a relatively weaker cutaneous response. Similar results were obtained with typhoid bacilli. Less frequent injections (every sixteen days) of hemolytic streptococci produced a more marked cutaneous sensitivity than more frequent ones (every four days).

SPECIES SPECIFICITY OF FIBRINOGENS. H. B. KENTON, J. Immunol. **25**:461, 1933.

On the basis of anaphylactic reactions in pigeons Kenton concludes that fibrinogens are not of identical structure in all species.

STREPTOCOCCUS LEUCOCIDIN. F. P. GAY and F. ORAM, J. Immunol. **25**:501, 1934.

Broth filtrates of a pathogenic hemolytic streptococcus contain a substance, "leukocidin," already described, that causes loss of phagocytic power, visible morphologic changes and loss of the power to reduce methylene blue in leukocytes of certain types and of certain animal species in varying degree.

ANTIGENIC SUBSTANCES OF CLOSTRIDIUM PARABOTULINUM. J. B. GUNNISON, J. Immunol. **26**:17, 1934.

Extracts of toxic cultures of Cl. parabotulinum prepared by the freezing and thawing of young washed cultures contained both protein and carbohydrate, but were not antigenic. These extracts reacted specifically in precipitin tests with antiserums produced by the inoculation of the intact organisms. An extract prepared from a strain of Cl. parabotulinum type B which had lost its toxicity was antigenic. This extract stimulated the formation of precipitins which were specific for the toxic type, but not for the groups within the type. Two protein substances were obtained from the supernatant fluid of 1 week old broth cultures by precipitation with acid. One of these substances (A), which was soluble in an excess of acid, was antigenic. The other (B), which was insoluble in an excess of acid, was nonantigenic. These substances (A and B) were not type-specific and did not stimulate the production of antitoxin.

FROM THE AUTHOR'S CONCLUSIONS.

THE DEPRESSION OF PHAGOCYTOSIS BY PRODUCTS OF STAPHYLOCOCCI. R. M. PIKE, J. Immunol. **26**:69, 1934.

Filtrates of staphylococci exert a depressing effect on phagocytosis in vitro. The depressing agent is not antigenic, is thermostable and does not deteriorate on standing. Its production is not affected by an atmosphere containing added carbon dioxide. A similar phagocytosis-depressing substance is produced by the colon bacillus.

FROM THE AUTHOR'S CONCLUSIONS.

PNEUMOCOCCAL HAEMOLYSIN. S. T. COWAN, J. Path. & Bact. **38**:61, 1934.

Hemolysin is found in the fluid part of young broth cultures of Pneumococcus. Hemolysin is not type-specific, and the capacity of a strain to produce hemolysin varies independently of virulence.

RICKETTSIA VACCINE IN TYPHUS. RUDOLF WEIGL, Arch. Inst. Pasteur de Tunis **22**:315, 1933.

A series of observations were made on persons vaccinated with the phenolized intestines of infected lice. A man, immune to typhus, was employed to feed laboratory lice daily. Without knowledge of Weigl, he gave several hundred to his wife to feed. She had been vaccinated. No attack followed, so several members of the institute repeated the accidental experiment. The results indicated the value of vaccination. One person, vaccinated too late, was attacked but still failed to transmit infection to lice. Thus prophylactic virtues are also claimed for the vaccine, since distribution of the virus through the blood is prevented. The latter observation was confirmed by animal experiment.

M. S. MARSHALL.

CROSS-IMMUNITY TESTS WITH A RODENT TYPHUS VIRUS FROM ANVERS. CHARLES NICOLLE and J. LAIGRET, Arch. Inst. Pasteur de Tunis **22**:338, 1933.

A virus, isolated from rats from the S. S. Roumanie, which arrived at Anvers March 21, 1933, was tested on guinea-pigs. Cross immunity was manifested against the historic Tunis strain of typhus virus, and against the rodent strains of Mexico and Toulon, but not against the virus of Rocky Mountain spotted fever. Four animals given the latter virus followed by the Anvers strain showed, as a result of the second virus, one clear infection, two light infections and one absence of infection. The viruses were reversed in five animals, resulting in one clear infection, three light ones and one failure or doubtful infection. Since, however, fresh animals usually die from the virus of Rocky Mountain spotted fever, it seemed that the Anvers virus antigenically approached the Montana virus more than other rodent strains thus far studied.

M. S. MARSHALL.

LOUSE FECES FOR RICKETTSIA VACCINE. B. CHRZANOWSKI and H. MOSING, Arch. Inst. Pasteur de Tunis **22**:346, 1933.

The authors prepared a vaccine from the feces of infected lice, purified by fractional centrifugation and washing. From experiments on about 250 guinea-pigs, with the classic Weigl vaccine for control, it was concluded that such vaccine immunized even in small doses (equivalent to the elimination from 2 lice in three days). One gram was sufficient to immunize from 600 to 1,000 animals. No reactions were observed. Feces 2 years old were still effective. It was estimated that the feces of lice during the last three days of infection included two thirds of the number of rickettsiae retained in the intestines during extreme infection. Agglutination occurred with rickettsiae in titers proportional to the amounts of vaccine. It is suggested that this vaccine be added to the intestines (Weigl's vaccine) in the proportion of 1 : 1.5, thereby reducing the laborious effort required in collecting those organs.

M. S. MARSHALL.

INFLUENCE OF THE VEGETATIVE NERVOUS SYSTEM ON ANAPHYLAXIS. G. GUASSARDO, Pathologica **25**:642, 1933.

Choline and ergotamine, which stimulate the vagus, increase the anaphylactic shock of guinea-pigs sensitized against horse serum if given during the whole period of anaphylactic incubation. Atropine and epinephrine, which stimulate the sympathetic, produce a contrary effect.

E. VON HAAM.

A STUDY OF STAPHYLOLYSIN. J. FORSSMAN, Biochem. Ztschr. **265**:291, 1933.

Forssman found a marked variation in the properties of filtrates of broth cultures of hemolytic staphylococci. The technic of the preparation of the lysin had some, though only limited, bearing on its hemolytic efficiency. The optimum conditions were: a 4 to 9 day old growth in veal broth containing from 4 to 7.5 per cent peptone and about 0.2 per cent of rabbit or sheep blood and a decreased supply of oxygen through the use of specially constructed stoppers. Guinea-pig blood and dextrose added to the medium were unfavorable. Staphylococci growing on blood agar plates are known to lake uniformly the red blood cells of a very large variety of animal species. The in vitro determination of the lytic power of filtrates revealed a marked and rather irregular variation. The red blood cells of guinea-pigs and horses were not laked and those of man only slightly, while those of the goat, sheep, ox and particularly the rabbit were readily hemolyzed. Variations were noted with different specimens of blood from the same individuals. Equally marked variations were caused by different degrees of temperature. The optimum temperature was 37 C. for two hours, followed by twenty hours at 10 C. The red blood cells of rabbits were laked at the end of the first period of incubation, while those of the other species showed then only very slight hemolysis or none, the main part of the lysis occurring during the subsequent incubation at the lower temperature. The laking of red blood cells is the only common feature of immune hemolysins and of staphylolysin. The effect of the latter is inversely proportionate to its dilution and directly proportionate to the concentration of the red blood cells, both properties being diametrically opposite to those possessed by immune hemolysins. Forssman's observations on the adsorption of staphylolysin by various red blood cells differ from those previously reported. He found no relation between the adsorption and the lysis; in other words, the adsorption occurred even with red cells known to be resistant to lysis and vice versa. The adsorption was irregular. A striking phenomenon was a marked but only temporary adsorption of the lysin at 0 C. by red blood cells of some species. The lysin was liberated into the fluid after very short periods of time. The latter quality, the increase of the lytic potency with an increase of the concentration of red cells, and the possible, though not definitely established, activation by the blood cells suggest that the staphylolysin is ferment-like.

I. DAVIDSOHN.

ALTERATION IN THE ANTIBODY FORMATION IN RABBITS. E. HAUSMANN, Frankfurt. Ztschr. f. Path. **45**:431, 1933.

Precipitins, agglutinins and hemolysins were produced in rabbits by injection of foreign serum and red blood cells respectively. While injections of epinephrine and pilocarpine did not cause any alteration in the production of antibodies, a definite increase in the formation of all the three antibodies was produced by the injection of atropine.

W. SAPHIR.

THE MODE OF ACTION OF IMMUNE SERUM IN SWINE ERYSIPELAS. DEZSÖ GAJZÁGÓ, Zentralbl. f. Bakt. (Abt. 1) **125**:89, 1932.

Gajzágó studied the effects of passive immunization of mice and pigeons with an antiserum for Erysipelothrix rhusiopathiae. He observed no bactericidal action and found no injurious effects on the micro-organisms. Phagocytes played the predominant rôle, although bacteriotropins were not exclusively concerned, inasmuch as serums in which bacteriotropins had been removed by saturation still were protective. Bacteria injected intraperitoneally into immune animals agglutinated in the peritoneal cavity and were more effectively phagocytosed than in normal animals. Furthermore, bacteria could be recovered from the blood stream of the normal animal for from one to two days, whereas in the immune animal the micro-organisms persisted in the blood stream only to the third hour.

PAUL R. CANNON.

THE EFFECT OF "BLOCKADE" OF THE RETICULO-ENDOTHELIAL SYSTEM ON THE COURSE OF VACCINIA. ALEXANDER HASSKÓ, Zentralbl. f. Bakt. (Abt. 1) **125**:166, 1932.

Rabbits were given intravenous injections of a 10 per cent solution of saccharated iron and after several weeks' treatment were infected via the scarified skin with raw vaccinial lymph, and the effects of generalization of the virus were compared with those observed in normal rabbits similarly affected. The virus generalized much more markedly in the "blockaded" animals, and the infection was much more severe. Many of the animals died from secondary infections. No quantitative differences in the concentration of virus in the blood of normal and "blockaded" rabbits were demonstrable, however, by inoculation of the blood into the scarified skin of guinea-pigs. Experiments on the effects of generalization of the virus in normal and splenectomized guinea-pigs, cutaneously infected, show a more marked generalization in the latter.

PAUL R. CANNON.

THE BORDET-WASSERMANN REACTION IN TYPHUS FEVER. L. HINSZFELD and W. HALBER, Acta path. et microbiol. Scandinav., supp. 16, p. 114, 1933.

The Wassermann reaction is not absolutely specific for syphilis. It may be positive in typhus, leprosy, trypanosomiasis, malaria, endocarditis lenta, measles and the last stages of cancer. A comparison was made of Wassermann reactions in syphilis and in typhus, using various antigens and absorption tests with lecithin. In syphilis there is a reagin against organ extracts. In typhus this could not be demonstrated. The theory of these phenomena is discussed.

JACOB KLEIN.

RELATION BETWEEN ALLERGY AND IMMUNITY IN TUBERCULOSIS. OLUF THOMSEN and K. PEDERSEN-BJERGAARD, Acta path. et microbiol. Scandinav., supp. 16, p. 521, 1933.

This is an attempt to solve experimentally the question whether allergy in the presence of tuberculous infection increases immunity and favorably influences resistance against superinfection as well as against the existing infection. A series of guinea-pigs was sensitized to horse serum. An emulsion of tubercle

bacilli in horse serum was then injected, and the results were compared with those in nonsensitized controls. The local anaphylactic reaction had no influence on the tuberculous process. Nor was there any favorable influence on superinfection.

JACOB KLEIN.

THE LEUKOCYTES IN ISO-AGGLUTINATION. IVAR WALLGREN, Acta path. et microbiol. Scandinav., supp. 16, p. 556, 1933.

Agglutination was carried out with whole blood in Tyrode's solution and 25 per cent serum. The preparations were examined in a warmed chamber with the dark field. Clumps of erythrocytes were found about leukocytes as a center. This did not seem to interfere with the viability of the leukocytes. When the agglutination ceased, the erythrocytes were taken up by the leukocytes. No agglutination of the leukocytes took place. In normal blood under these conditions auto-erythrophagocytosis takes place. There are serums which stimulate this process. B-serum and A-B serum induced phagocytosis of B-erythrocytes and also O-erythrocytes. This would not happen were the isohemopsonins group-specific. The agglutinins and the opsonins are not identical.

JACOB KLEIN.

Tumors

EFFECTS OF THYROIDECTOMY ON TUMOR GROWTH IN MICE. M. LEVINE and V. H. KUGEL, Am. J. Cancer **19**:817, 1933.

The general tendency seemed to be for the thyroid-injured mouse to show smaller tumors than the control although the weight of the animal was favored by the thyroid injury.

AMYLOIDOSIS IN MULTIPLE MYELOMA. O. S. RANDALL, Am. J. Cancer **19**:838, 1933.

A case of multiple myeloma of bone is reported in which amyloid infiltration of the small intestine resulted in intestinal obstruction. Although amyloidosis of the intestine is rare as a complication of multiple myeloma, one should at least suspect it when complaints referable to the gastro-intestinal tract are made. Inasmuch as gastro-intestinal symptoms are reported in 20 per cent of all cases of multiple myeloma (Geschickter and Copeland), amyloidosis of the intestine may be a more frequent complication than is generally believed. Amyloidosis should be considered in every wasting and long-standing illness, whether or not suppuration is present.

FAILURE OF ETHYL ALCOHOL IN MOUSE CANCER. M. C. MARSH, Am. J. Cancer **19**:847, 1933.

Ethyl alcohol was administered in various concentrations, at maximum dosage, over long periods, by intravenous and subcutaneous injections, by ingestion and by combinations of these, to forty-nine mice with spontaneous tumors. There was no evidence of any curative effect.

AUTHOR'S SUMMARY.

METAPLASTIC AND NEOPLASTIC BONE- AND CARTILAGE-CONTAINING TUMORS OF SOFT PARTS. T. B. MALLORY, Am. J. Path. **9**:765, 1933.

Many apparent bone-containing and cartilage-containing tumors of soft parts are in reality of metaplastic rather than neoplastic origin. Extreme care may be requisite to differentiate the active stage of osteoblastic or chondroblastic metaplasia from malignant neoplasia. Certain bone-forming spindle cell sarcomas of soft parts may more logically be regarded as fibrosarcomas with metaplastic foci of osteogenesis than as true osteoblastomas.

AUTHOR'S CONCLUSIONS.

CONGENITAL LYMPHOBLASTOMA. C. F. BRANCH, Am. J. Path. **9**:777, 1933.

The literature concerning cases of congenital lymphoblastoma is reviewed. A case of congenital lymphoblastoma is presented in which the normal architecture of the organs had been virtually destroyed by a massive lymphocytic infiltration.

AUTHOR'S SUMMARY.

THE ANGLE OF THE MITOTIC SPINDLES IN MALIGNANT CELLS. S. WARREN, Am. J. Path. **9**:781, 1933.

On the basis of the cases thus far studied the angle of the mitotic spindle provides a criterion by which carcinoma can be distinguished from sarcoma and from lymphoblastoma. Because of the two types of mitosis apparently usually occurring in the same tissue in fibrosarcoma, as distinct from other types of sarcoma, this particular form may be distinguished. The mean values obtained for the mitotic angles are: in carcinoma, 91 degrees; in melanotic sarcoma, 56 degrees; in fibrosarcoma, 72 degrees for the narrow spindles and 108 degrees for the wide spindles; in osteogenic sarcoma, 69 degrees, and in Ewing's tumor, 88 degrees. Further study of other types of tumors and normal cells is now in progress.

AUTHOR'S SUMMARY AND CONCLUSIONS.

THE EFFECT OF CAESIUM CHLORIDE ON TRANSPLANTED TUMORS OF MICE. A. W. WRIGHT and C. F. GRAHAM, Am. J. Path. **9**:789, 1933.

The hypothesis that the introduction of strongly basic ions into the nuclear complex might greatly reduce nuclear activity is not supported by the study of the effect of cesium on the growth of the Twort carcinoma. There is no evidence that it affects in any way the capacity of the tumor cells to divide and multiply. There is, however, suggestive evidence to indicate that necrosis of the neoplastic tissue may be more extensive in the cesium-treated animals. That cesium under certain conditions has a deterrent effect on the growth of the tumor is indicated, and further studies of this property of the element are in progress.

AUTHOR'S SUMMARY AND CONCLUSIONS.

THE DIAGNOSIS OF TUMORS BY ASPIRATION. F. W. STEWART, Am. J. Path. **9**:801, 1933.

Needle aspiration is an expeditious practical method for the diagnosis of tumors. In approximately twenty-five hundred cases my associates and I have observed no untoward result following its use. The interpretation of smears of aspirated material often requires competent clinical assistance. Diagnosis by aspiration is as reliable as the combined intelligence of the clinician and the pathologist makes it. The pathologist who ventures to interpret the material obtained by aspiration will have to revise or relearn many criteria. The clinician must appreciate how far the pathologist can logically go in interpreting the smear. Both must maintain a sympathetic attitude toward a new procedure. In the institution with which I am associated the method has so established its usefulness that it has acquired a permanent place as a means of diagnosis.

AUTHOR'S SUMMARY.

PRECANCEROUS EPIDERMAL LESIONS. M. B. SULZBERGER and D. L. SATENSTEIN, Arch. Dermat. & Syph. **28**:798, 1933.

A man, aged 39, had had a lesion on the glans penis for three months. It continued to spread. The lesion consisted of erythematous plaques from which tiny droplets of clear fluid exuded. Biopsy showed hyperplastic epidermis, intracellular and intercellular edema and vacuolation. The superficial dermis showed vascular dilatation and marked infiltration by round cells, plasma cells and

eosinophils. The lesion should be considered as precancerous and treatment should be destructive. In dermatologic literature this condition is called erythroplasia of Queyrat.

S. W. BECKER.

TUMORS OF THE SYMPATHETIC NERVOUS SYSTEM: NEUROBLASTOMA, PARAGANGLIOMA, GANGLIONEUROMA. D. LEWIS and C. F. GESCHICKTER, Arch. Surg. **28**:16, 1934.

These three types of tumors are regarded as developing from cells which wander out from the neural crest during embryonic life. The undifferentiated cell may give rise to neuroblastoma and the more differentiated to paraganglioma and ganglioneuroma. All three types of growth in the same tumor indicate a common origin.

LYMPHANGIO-ENDOTHELIOMA OF BONE. D. A. DESANTO, Arch. Surg. **28**:66, 1934.

A tumor is described which is traced to the perivascular lymphatics of the haversian canals and subperiosteal tissue. This tumor fulfils every criterion of the so-called Ewing's tumor of bone.

THE AGENTS IN ANILINE CARCINOMA OF THE BLADDER. G. H. GEHRMANN, J. Urol. **31**:126, 1934.

Tumor of the bladder occurs more frequently among dye workers than among workers not in contact with dyes, and in my experience it occurs to the extent of 4.5 per cent. The combined experiences of the dye industries of Germany, Switzerland, England and America indicate that probably aniline, *alpha* and *beta* naphthylamine and benzidine are the etiologic compounds. Tumor of the bladder may appear any time after two years' exposure, and removal from the dye operation does not eliminate the possibility of future developments. The adoption of a completely closed and properly ventilated process, together with careful medical supervision and protection, will eliminate the hazard, but these methods will require many years of active enforcement and must continue as long as the compounds are made.

FROM AUTHOR'S SUMMARY.

GENESIS OF ANILINE CARCINOMA OF THE BLADDER. D. M. GAY, J. Urol. **31**:137, 1934.

Whether the injurious agent exerts its first effect on the submucous blood vessels or directly on the epithelium cannot be proved with the material at hand; but I hold to the hypothesis that aniline tumors are caused by an agent to which the tissues of the bladder are specifically vulnerable. Although the greatest changes are in the region of the trigon, the multiplicity and subsequent origin of tumors in different sites lead me to believe that the injury involves the entire bladder, probably owing to the circulation of a cancerogenic agent in the blood.

FROM AUTHOR'S SUMMARY.

THE EFFECT OF HYPOPHYSECTOMY ON THE GROWTH OF THE WALKER RAT TUMOUR. C. S. MCEUEN and D. L. THOMSON, Brit. J. Exper. Path. **14**:384, 1933.

The growth of the Walker rat tumor in the young male albino rat is retarded by hypophysectomy, and the resistance of the animal is lowered. Metastases occur less frequently in hypophysectomized rats, probably because large tumors are rare. Inoculation into hypophysectomized rats is successful in a large proportion of cases, but the growth of the transplants is slow. The total weight of the hypophysectomized tumor-bearing rat remains constant but that of the control is increased. If this increase is prevented by restricting the intake of food, the growth

of the tumor is retarded. This retardation is not significantly less than that produced by hypophysectomy. The body weight of the rat minus the tumor tends to decrease; this decrease is approximately equal to the weight of the tumor in the hypophysectomized rat, but not in the normal rat.

AUTHORS' SUMMARY.

THE REACTION OF THE ARTERIAL BLOOD IN CANCER. SYLVIA DICKINSON and R. E. HAVARD, Brit. J. Exper. Path. **14**:394, 1933.

The results of previous workers are summarized and discussed. The technic is described for collection of samples of arterial blood from patients with and without malignant diseases, and for measurement of the p_H of the blood at 37 C. by two independent glass electrodes. The results support the conclusion that the blood of patients with malignant disease of the mouth or skin, or with secondary conditions of the glands, is not more alkaline than that of patients free from malignant disease. An experiment is described which demonstrated that momentary alterations of respiration can affect the p_H of the blood.

AUTHORS' SUMMARY.

ON THE NATURE OF THE TUMOURS INDUCED IN FOWLS BY INJECTIONS OF TAR. JAMES MCINTOSH, Brit. J. Exper. Path. **14**:422, 1933.

Tumors of sarcomatous type can readily be induced in the fowl by intramuscular injections of tar and lard. Four tar-induced tumors have been transmitted in series in fowls by injections of tumor emulsion, and three of these have been transmitted by means of cell-free filtrates (Berkefeld). Tar-induced sarcomatous tumors of the fowl conform closely in morphologic and biologic characteristics with the naturally occurring sarcomatous tumors of the fowl.

AUTHOR'S SUMMARY.

BONE FORMATION IN CARCINOMA OF THE GALLBLADDER AND IN ITS METASTASES. G. MICSEH, Frankfurt. Ztschr. f. Path. **44**:430, 1933.

The primary carcinoma of the gallbladder as well as metastases in the lungs, liver and lymph nodes showed typical bone and bone marrow formation. The presence of cancer cells apparently stimulated proliferation of connective tissue. The newly formed mesenchymal cells were then secondarily transformed into bone and bone marrow cells as the result of metaplasia due to a specific stimulation of the carcinoma cells.

WILLIAM SAPHIR.

THE RELATION OF THYROID ADENOMA AND GOITER TO THE CAPSULE OF THE THYROID AND TO ITS BLOOD VESSELS. F. DOEPFNER, Frankfurt. Ztschr. f. Path. **44**:461, 1933.

Four instances of so-called metastasizing thyroid adenoma, seventeen instances of simple thyroid adenoma and four of proliferating goiter have been studied. In nearly all cases an invasion into the connective tissue capsule of the thyroid gland was noted. In the four cases of metastasizing adenoma, in three of the instances of simple adenoma and in three of the cases of proliferating goiter tumor tissue had broken into the veins. These observations lead Doepfner to believe that invasion of tumor tissue into blood vessels does not always of itself lead to metastases, but that certain other factors, such as age of the patient, play an important rôle in the production of metastases.

WILLIAM SAPHIR.

MYELOID CHANGES IN THE SPLEEN OF MICE TREATED WITH TAR. N. WATERMAN, Frankfurt. Ztschr. f. Path. **44**:540, 1933.

Waterman calls attention to the myeloid transformation of the spleen regularly found in the mouse with tar carcinoma. Since this change is never observed in the mouse with tar papilloma it is assumed that tar cancer can develop only when myeloid changes in the spleen have taken place.

WILLIAM SAPHIR.

Medicolegal Pathology

OXIDATION OF ALCOHOL WITH RELATION TO MEALS. GOTTFRIED JUNGMIEHEL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **22**:11, 1933.

If alcohol is ingested on a fasting stomach there is a greater concentration in the blood after drinking pure diluted alcohol than after drinking beer. With a previous intake of food there is a diminution of alcohol in the blood due to the altered conditions of absorption from the gastro-intestinal tract. A moderate caloric intake is associated with a greater oxidation of alcohol than an excessive intake of food.

JACOB KLEIN.

EXPERIMENTAL STUDIES ON DEATH FROM DROWNING. NICOLAE P. BALAN. Deutsche Ztschr. f. d. ges. gerichtl. Med. **22**:167, 1933.

Brouardel distinguishes five phases in the act of drowning: (1) excitement, (2) apnea, (3) deep inspiration, (4) asphyxia and (5) terminal inspirations. Some investigators doubt that water enters the lungs in drowning, and state that death is due to pulmonary edema. To clarify this question experiments were done on twenty guinea-pigs in water containing a suspension of rice flour, which is readily seen under the microscope. After drowning the lungs were removed and studied. The rice granules were not found in the lung until the third or dyspneic stage. The water first entered the upper part of the lung; intensive inspiration drew it into the lower lobes. Previous views are corroborated that water enters the respiratory passages and lungs during drowning, especially in the period of dyspnea, and that death is due to the resulting asphyxia.

JACOB KLEIN.

OBSERVATIONS ON EXECUTION BY HANGING. E. KALLE, Deutsche Ztschr. f. d. ges. gerichtl. Med. **22**:192, 1933.

Observations on twenty-four persons executed by hanging indicate that death does not occur suddenly; that pulse and cardiac activity may be noted even twenty minutes afterward. The strangulation causes severe injuries to the structures in the neck. Fracture or luxation of the cervical vertebrae is most rare. Reflex muscular activity is frequently observed and not to be ascribed to conscious movement. The period of deepest unconsciousness occurs at the moment of the drop when the loop begins to act.

JACOB KLEIN.

ROENTGEN DEMONSTRATION OF A METAL RING AT THE POINT OF ENTRANCE OF A BULLET. L. M. EIDLIN, Deutsche Ztschr. f. d. ges. gerichtl. Med. **22**:204, 1933.

Roentgen examination demonstrates a lead ring at the point of entrance of a lead bullet. With a steel jacket bullet the metal ring is present in the skin with a shooting distance of 25 to 40 mm. The metal ring aids in distinguishing between the points of entrance and exit of the bullet. Contamination of the wound with blood, organic materials and cleaning of the clothing does not interfere with the demonstration. This marking may be the only available information as to the type of weapon, the distance of the weapon and the direction of the shot. The metal ring is less definite with a wound from a cleaned or a new weapon than with a used or an unclean one. The angle of inclination of the weapon may also be determined in this way. The advantages of this method are: simplicity, availability, noninterference with other examinations and accuracy.

JACOB KLEIN.

PERFORATION OF THE DRUM MEMBRANE AND DEATH FROM DROWNING. M. MILOVANOVIC, Deutsche Ztschr. f. d. ges. gerichtl. Med. **22**:427, 1934.

A thorough examination of sixty-seven cases of drowning did not yield any evidence supporting the view of a causal connection between perforation of the drum membrane and death from drowning.

ACUTE VERONAL POISONING. S. SCHEIDEGTER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **22**:452, 1934.

In two cases of death from acute veronal poisoning distinct changes due to anemia appeared in the ganglion cells a few hours after the poison was taken. The lipoid changes in the ganglion cells and glia were pronounced. A smaller degree of lipoid accumulation was observed also in the endothelial cells of other organs and in the Kupffer cells.

ELECTRIC INJURY AND DEATH. S. KOEPPEN, Virchows Arch. f. path. Anat. **290**:460, 1933.

A young electric worker who, in the course of his work, had been subjected to repeated minor electric shocks that caused no immediate damage began to have symptoms of multiple sclerosis and half a year later died. Autopsy revealed multiple older areas of softening in the brain and recent thrombosis of the sigmoid sinus. Nothing could be found that might explain these lesions. This case raised questions relative to late injury by the electric current. These, as well as controversial questions on the immediate injury caused by electricity and on the mechanism of death, were subjected to experimental investigation. Guinea-pigs, rabbits and dogs were used. The direct current was used, at a strength of 20 to 70 volts in smaller animals and up to 220 volts in larger animals. Single shocks and repeated shocks of one to thirty seconds' duration were applied. In some animals the current was applied at intervals of a month with the aim of producing late changes; the results of such experiments are not included in this report. The positive electrode was usually placed on the head, the negative one on the thigh. Some animals died as the result of the shock and were subjected to immediate gross and microscopic examination. Others that did not die were killed after application of the current and examined. Still others were permitted to live and were killed at varying intervals. Koeppen recognizes local and general effects of the current. The local effects were edema, loss of hair, necrosis, ulceration and infection. Edema and loss of hair are the result of vascular reactions, such as predominate in the general effects of the current. Necrosis and the formation of spaces in the epithelium are specific electric effects due to electrolysis; they are not due to burning or heat; the heat generated in the tissue by the weak currents used was measured and found to be within the limits of the normal production of heat by the tissue. Infection is secondary to death of tissue. The chief and essential general or distant effect is the vascular reaction. This is characterized by extreme distention of the capillaries and veins, with hyaline and red cell thrombosis and diapedesis of red corpuscles. The arteries are contracted. This vascular reaction Koeppen interprets, in accordance with the theories of Ricker, as a stasis paralysis of the capillary bed and a spasmodic contraction of the arterial system which is carried back to the heart. The coagulation time of the blood is decreased, and the viscosity is increased. The cerebral effects, which manifest themselves as an epileptiform seizure with loss of consciousness, are due not to the direct action of the current on the brain, but to the vascular reaction of the cerebral vessels, which is the same here as in the other organs. This contention is proved by the fact that animals decerebrated above the thalamus, in which there was no cerebrum to be directly affected by the current, presented exactly the same manifestations as those with intact brains. Koeppen concludes that the local effects of the electric current are specific and are due to electrolysis. They may be complicated or overshadowed by burns if the current is strong enough or if arcing occurs. He maintains that death is due, not to the effect of the current on the brain or to asphyxia, as Jellinek, Schridde and others have claimed, but to the cardiovascular reaction induced by the current. The therapeusis of electric shock therefore requires not only artificial respiration, but agents that will relieve the arterial spasm.

O. T. SCHULTZ.

PREGNANCY AND RUPTURE OF THE AORTA. H. UEBERMUTH, Zentralbl. f. Gynäk. **57**:1633, 1933.

Including the case reported in this article there appear to be recorded in the literature only eight cases of rupture of the aorta in pregnancy. The ruptures occurred at the end of pregnancy on the basis of atherosclerotic or syphilitic changes in the vessel. It is pointed out that aneurysm oi the aorta is a clearcut indication for the interruption of pregnancy.

THE USE OF ALCOHOLIC SUSPENSIONS OF SPIROCHAETA PALLIDA FOR THE SEROLOGIC DIAGNOSIS OF SYPHILIS. R. R. HOELTZER, Ztschr. f. Immunitätsforsch u. exper. Therap. **80**:368, 1933.

Spirochaeta pallida was suspended in a solution of alcohol in physiologic solution of sodium chloride. The suspension was used as an antigen for the complement fixation test for syphilis. It did not become anticomplementary during a period of twelve months, and it became only moderately less sensitive. In a comparative study with other methods the Kahn test proved more sensitive but slightly less specific, while all other antigens were less sensitive than the one prepared from spirochetes.

I. DAVIDSOHN.

NITROBENZENE POISONING. GUNNAR AHLGREN, Acta path. et microbiol. Scandinav., supp. 16, p. 6, 1933.

A medical student died four and one-half hours after the ingestion of nitrobenzene with suicidal intent. Death was due to respiratory failure. The oxygen capacity of the blood was 7.8 per cent one-half hour before death. The urine withdrawn from the bladder after death contained no albumin, reducing substance, blood pigment or sediment. Autopsy was not done. Experiments on dogs indicated an early anuria, although the kidney showed no histologic change. This would explain the finding of normal urine. The clear urine had been excreted before the ingestion of nitrobenzene, which had rapidly caused anuria.

JACOB KLEIN.

THE BLOOD GROUP QUALITIES IN HUMAN URINE AND THEIR CONCENTRATION AND QUANTITATIVE DETERMINATION. ERIK JORPES and GUNNAR NORLIN, Acta path. et microbiol. Scandinav. **11**:91, 1934.

The urine was concentrated by evaporation, dialysis and precipitation with alcohol; 120 Gm. of dry water-soluble substance was obtained from 180 liters of A urine and 155 Gm. from 240 liters of B urine. The quantities of the A or B substance in such concentrates before and after various procedures were determined by adding them in watery solution to human iso-agglutinating serums and by subsequently determining the decrease of the iso-agglutinating properties of such serums. The blood group qualities proved highly heat-resistant (no change after one-half hour at 100 C.). They were also able to resist the action of acids, but were quickly destroyed by alkalis. Jorpes and Norlin interpret the latter finding as speaking against the hypothesis of a polysaccharide nature of the blood group substances, for polysaccharides are known to be particularly resistant to alkalis, while a racemization of proteins by alkalis destroys their antigenic properties.

I. DAVIDSOHN.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, April 9, 1934

E. H. HATTON, *President, in the Chair*

THE SOURCE OF CALCIUM CARBONATE IN GALLSTONES. D. B. PHEMISTER.

The three principal constituents of gallstones are cholesterol, bile pigment and calcium carbonate. These substances may be present singly or in combinations giving a variety of stones. The pigment is derived from bile. There has been much difference of opinion as to the source of the calcium carbonate and the cholesterol. Some claim that they come from the bile, and others, that they are secreted by the wall of the gallbladder. A series of cases of gallstones and experiments on animals have shown that calcium carbonate is thrown out into the gallbladder when the cystic duct or ampulla is obstructed. In eighteen cases of either marked or complete obstruction by an ordinary gallstone calcium carbonate was precipitated in the gallbladder in amounts varying from 0.5 to 20 Gm. It was present as a paste mixed with mucus, as a coarse sand or as large white stones in the most marked cases. In some cases the calcium carbonate incorporated other stones. The surface deposits on stones in the gallbladder have also been found to be laid down in the presence of duct obstruction. Additional evidence that the layers of calcium carbonate in mixed stones are associated with duct obstruction is obtained from cholecystography. When the gallstones cast ring shadows in x-ray pictures owing to the presence of calcium, the gallbladder does not become visualized with cholecystography. Nuclear deposits of calcium in gallstones are more difficult to explain, and there is greater uncertainty as to the source of the calcium. An inflammation in the gallbladder interfering with free filling and with concentration of the bile may be responsible for the precipitation of calcium forming nuclei on which subsequent deposits of pigment and cholesterol are made.

DISCUSSION

E. F. HIRSCH: When the cystic duct is ligated, is there a shift in the reaction of the fluid contained in the gallbladder?

D. B. PHEMISTER: Yes, there is an increase in the alkalinity.

GENERALIZED ANGIOSARCOMA OF THE LYMPH NODES. PERRY J. MELNICK.

An unusual case of generalized angiosarcoma of the lymph nodes of eighteen months' duration in a 64 year old white man was reported. Biopsies of four different lymph nodes revealed the same structure, namely, an angiofibromatous tumor of low malignancy, centrally located in the lymph nodes, fairly well encapsulated, and appearing independent of the lymphatic tissue or the reticulo-endothelial tissues. The origin seemed to be from multiple foci of angiofibroma in the lymph nodes. The relationship to other forms of multiple angiomatosis and to Kaposi's multiple angiosarcomatosis of the skin was discussed. Three similar cases of generalized sarcomatosis of the lymph nodes have been reported previously.

DISCUSSION

P. DELANEY: The presentation is confused because the primary focus, whether hemangiomatous or lymphangiomatous, is not disclosed.

P. J. MELNICK: The comments by Dr. Delaney are true, for the material is entirely surgical and there has been no postmortem examination.

SIMULTANEOUS OCCURRENCE OF TWO TUMORS (GLIOMA AND SARCOMA) IN THE CEREBRAL HEMISPHERE OF A CHILD. PERCIVAL BAILEY and ADOLFO LEY.

We have found only two accounts of the simultaneous occurrence of glioma and sarcoma in the same cerebrum, one by Merzbacher and Uyeda and the other by Wohlwill. The condition seems sufficiently rare to justify a brief report.

Our case occurred in a boy, aged 6 years, who complained of headaches a few weeks before admission to the hospital. He had symptoms of increased intracranial pressure and left spastic hemiparesis. An osteoplastic exploration was made, and a large amount of tumor tissue was removed from the temporal lobe through a transcortical incision. He recovered promptly but acquired otitis media, after which he began to have convulsions, and the site of the operation became tense and bulging. It was reopened and more tumor tissue removed, but the child gradually failed and died.

Aside from the suppuration in the middle ear, necropsy disclosed bilateral fibrous obliterative pleuritis and remnants of tumor in the right temporal lobe of the brain, extending back to the occipital region. In addition there were an extensive ependymitis of all the cerebral ventricles and a small abscess in the old operative wound of the brain.

The tumor removed at the first operation was definitely sarcoma. It was cellular, swarming with mitotic figures. Around the blood vessels were rings of reticulin extending out for some distance into the tissue. The nuclei were vesicular, and in some parts the cells were spindle-shaped with numerous reticulin fibrils between the cells. When the tumor removed at the second operation was examined, we were surprised to find in some portions a structure that was definitely glioma. Here no mitoses were seen, the cells were definitely astroblasts, and the reticulin was confined strictly to the walls of the blood vessels.

At necropsy, in the occipital region, the two tumors could be clearly distinguished. On cross-section, the sarcoma was firm, white and smooth, and the glioma was gray, soft and granular.

The sarcoma must have been of more recent origin, to judge by the numerous mitoses which it contained.

A complete description of the tumors with numerous illustrations will be published in the *Archivos de neurobiologia*.

DISCUSSION

E. F. HIRSCH: What tissues do you think gave rise to the sarcoma?

P. BAILEY: The sarcoma may have originated from tissues in or about blood vessels.

INTESTINAL OBSTRUCTION BY A SUBMUCOUS LIPOMA. J. D. KIRSHBAUM.

In a series of 5,754 autopsies at the Cook County Hospital since 1929 there were 9 lipomas of the gastro-intestinal tract. Two of them were submucous and produced symptoms of intestinal obstruction. The first case revealed at autopsy a sequestration of a mobilized lipoma in the lower ileum causing obstruction and diffuse peritonitis. The second case presented at operation an intussusception of the lower 8 inches (20 Cm.) of the ileum into the cecum. On release of the bowel a submucous lipoma in the ileum was resected. The patient died four days later, and the postmortem examination revealed acute generalized peritonitis. Both patients were ill for only two days: one, a man aged 43 years, and the other, a woman aged 42 years. Lipomas were third in frequency among the 47 benign tumors found in the 5,754 necropsies.

Regular Monthly Meeting, May 14, 1934

E. H. HATTON, *President, in the Chair*

THE RÔLE OF THE AVIAN TUBERCLE BACILLUS IN THE ETIOLOGY OF HODGKIN'S DISEASE. PAUL E. STEINER.

Diseased lymph node and splenic tissues from 15 patients with Hodgkin's disease (lymphogranulomatosis) together with tissues from 8 patients with other lymphomas were investigated (1) for the ability of the diseased tissues to produce tuberculosis in chickens, guinea-pigs, rabbits, dogs and mice, and (2) for the disease-producing capacity of these tissues as grafts. Diseased tissues from the 23 patients were injected or transplanted into 199 animals. An additional group of 23 chickens without injections served as controls of environmental factors, especially of spontaneous tuberculosis. A group of 8 dogs received intracerebral injections. The animals survived for periods varying from nine to thirteen months. Criteria for the diagnosis of tuberculosis in the animals were: (1) the acquisition of a positive tuberculin reaction; (2) characteristic gross and microscopic morphologic structures; (3) the presence of stainable acid-fast bacilli in suspicious lesions; (4) the growth of acid-fast bacilli from such lesions on culture mediums; (5) the production of tuberculosis in animals in passage experiments.

In the entire group of animals into which the diseased human tissues were injected, tuberculosis occurred in 1 chicken and 1 guinea-pig given injections of tissue showing Hodgkin's disease and in 1 guinea-pig given an injection of lymphosarcomatous tissue. Animals which received injections of material from tuberculous adenitis became diseased. In the diseased chicken, a spontaneous infection was not excluded. In passage experiments with tissues from the infected animals, tuberculosis was produced.

Numerous lesions in diseased chickens superficially suggesting tuberculosis were considered nontuberculous because they did not satisfy the five criteria mentioned.

No evidence was found that the diseased human tissues were transplantable or that they were capable of inducing lesions with a similar histologic structure in animals.

No strains of acid-fast bacteria were grown by modern cultural methods from tissues of patients with Hodgkin's disease. Likewise the occurrence of acid-fast forms of bacteria reported to exist transiently early in the cultures of such tissues was not confirmed.

Tuberculin protein (T. P. T., Seibert) was used in making intracutaneous skin tests on 35 patients with Hodgkin's disease, and on 38 control patients with a variety of lymphomas. Tuberculin proteins prepared from both avian and human strains were used in comparative quantitative tests for the purpose of obtaining information on the possible etiologic rôle of the avian tubercle bacillus in Hodgkin's disease.

No evidence of specific sensitization to the avian tuberculin protein was obtained by these tests. A marked desensitization (or absence of sensitization) was found to both proteins in the patient with Hodgkin's disease. This decreased "normal adult sensitization" had diagnostic value, especially in differentiating tuberculous adenitis. The incidence of absence of sensitization was greater in the Hodgkin's disease group than in the few with other lymphomas.

These tests suggest that either Hodgkin's disease desensitizes its victims to human and avian tuberculin proteins or it occurs usually in persons who are unable to acquire normal sensitization to these proteins. It is difficult to understand how either of these phenomena could occur in a disease unrelated to tuberculosis.

Within the limits of the adequacy of the testing methods used the avian tubercle bacillus seems to be eliminated as an etiologic factor in Hodgkin's disease. The absence of sensitization to the avian and human tuberculin proteins suggests that

some organism antigenically related to the tubercle bacillus might be etiologically involved. The investigation is being continued with this in mind.

(A complete report of part of this work appeared in the June issue, p. 749.)

DISCUSSION

PAUL R. CANNON: Have you noticed a similar decreased sensitization to other substances in patients with Hogkin's disease?

L. E. DAY: It would be interesting to correlate data on the geographic distribution of avian tuberculosis in the United States with similar data on the incidence of Hodgkin's disease. In North America there is no avian tuberculosis, or very little, along the Atlantic Coast. The Middle West has a great deal. If the two diseases are related etiologically, the geographic distribution should be similar. Do you recall whether the lesions observed along the intestinal tract in fowls were in males or in females? The bacillus of white diarrhea is carried by the females and is transmitted through the eggs.

PAUL E. STEINER: There seems to be no peculiar geographic distribution of Hodgkin's disease. Rural and urban inhabitants appear to be equally affected. Decreased sensitization does not seem to be associated with Hodgkin's disease. So far as I recall, the lesions along the intestinal tract were in both male and female chickens.

AN EXPLANATION FOR NORMAL DAILY VARIATIONS IN THE RATE OF SEDIMENTATION OF ERYTHROCYTES. EMIL T. HOVERSON.

Although the erythrocyte sedimentation test has been generally accepted both in Europe and America as a means of arriving at a diagnosis of the clinical activity of certain infectious diseases, its value in this connection has been doubted. Moreover, some fundamentals have been contradicted; for example, Pinner and his co-workers in tuberculosis disproved the belief that a rapid rate indicates an acute infection, and that a decreased rate connotes improvement. Variations in the rate have been noted by many, but since the specimens of blood were from patients who were known to be infected, the variations were ascribed to the acuteness of the disease. Pinner and Greisheimer found marked variations in normal persons.

The divergence of the opinions and reports on the subject is evidently not due to the difference in the methods used in making the tests, for Greisheimer observed a fairly close correlation between the methods of Cutler, Westergren and Linzenheimer and the procedures in each are standardized.

In an effort to arrive at definite conclusions regarding the cause of the variations in the rate, the work discussed here was undertaken. As a basis, the changes in chemistry, physiology, etc., observed by Petersen in connection with his meteorological studies might account for an actual state of the blood, and this in turn would affect the rate. Such changes which occur in normal persons have been worked out in detail, and were found to coincide with tropical or polar fronts (a polar front exists when the barometer is high and the temperature low, and a tropical front exists when the barometer is low and the temperature and the humidity high). If the chemistry, activity and other conditions change, there ought also to be a change in the rate of sedimentation of the erythrocytes. Accordingly, this work was planned to determine the variations and to correlate them with the meteorological conditions present at the time the determinations were made. The Linzenheimer method was used. Uniform conditions prevailed. All but two patients had the usual findings in dementia paralytica. One of these had a positive Wassermann reaction only of the serum; the other, a negative reaction of the serum and of the spinal fluid. The study extended from January 28 to March 1, 1934, and was so arranged that two or more patients were under observation throughout the interval. During this period nine distinct disturbances in meteorological conditions occurred. Five of these were designated as polar fronts and the

others as tropical fronts. Examination of the percentage variations in each patient's record shows that usually definite changes occurred with the weather changes. The effect of the weather changes was cumulative in two.

In certain patients the rate of settlement whether fast or slow was determined apparently by the character of the weather disturbance. Except for two patients in whom the effect was cumulative, the percentage variations in all of the patients tended to group themselves about an average percentage.

INVOLVEMENT OF THE MYOCARDIUM IN TUBERCULOSIS. HENRY HORN.

Although tuberculosis of the pericardium with extension to the myocardium is common, isolated myocardial tuberculosis is rare. Norris found only 6 cases in 1,764 persons with tuberculosis. Valentine, among 3,203 cases of generalized tuberculosis reported by various authors, found 7 with myocardial lesions. Only about 200 instances are mentioned in the literature. The types of myocardial involvement are: nodular, miliary and diffusely infiltrative. The nodular type is the most common. The nodules vary from pea-size to egg-size and some are so large as to obstruct the auricular flow of the blood. The number varies; in one reported case 18 nodules were found. They are usually round, yellowish-white and firm, and frequently well circumscribed. Ulceration is rare, but has been reported, and twice has been the cause of generalized miliary spread.

The miliary type is less common. Reference is made only to instances in which miliary tubercles were found exclusively in the myocardium. Up to 1906 only 41 reports of this finding were known. Since then 7 additional ones have been recorded. Much controversy has been waged over the incidence of miliary tubercles of the myocardium and generalized miliary tuberculosis. Weigert, Kaufmann and Maresch thought that the presence of miliary tubercles of the myocardium with generalized miliary tuberculosis was frequent. Such a conclusion is rendered doubtful, however, by a statistical review. Simmonds, for example, in 1879, in a study of 125 bodies with miliary tuberculosis, did not find a heart with miliary tubercles. Boltz in 1890 found 11 in 176, and Reichenbach, in 1896, found 4 in 85 bodies with tuberculosis. The tubercles either in the auricle or in the ventricle are of millet-seed size and semitransparent, and frequently follow blood vessels.

The diffusely infiltrative type is even less common and usually is associated with pericarditis. Grossly the myocardium is a white or uniformly gray to yellowish-gray firm tissue. The histologic structure occasionally presents diagnostic difficulties. Usually there is a granulation tissue with lymphocytes, polymorphonuclear leukocytes, giant cells of the Langhans type, and endothelial cells.

Some investigators, particularly the French, recognize still another form of myocardial tuberculosis: interstitial tuberculous myocarditis. The etiology is doubtful, and there are no morphologic characteristics of tuberculosis. In such cases, most authors consider the diagnosis of tuberculous myocarditis on morphologic evidence alone extremely hazardous and, therefore, this form is not considered in my classification.

Among 34 cases of generalized miliary tuberculosis in which the heart was examined carefully there were 3 with miliary tubercles of the myocardium. All three patients were within the first decade of life.

A boy, aged 7 months, had an old tuberculous bronchopneumonia and an acute miliary tuberculosis of the lungs, liver, spleen and leptomeninges. The heart was grossly normal. A granuloma histologically tuberculous was found. Acid-fast bacilli were not demonstrated by suitable stains.

A boy, aged 3 months, had tuberculous bronchopneumonia of the left lower lobe and acute miliary tuberculosis of the lungs, liver, spleen, kidneys, meninges and myocardium. The myocardium of the left ventricle had a few pearl-gray nodules the size of millet seeds. Histologically the nodules were tuberculous. A few acid-fast bacilli were found.

A girl, aged 10 years, had an old tuberculous bronchopneumonia of the right lower lobe and acute miliary conglomerate tuberculosis of the lungs, liver, spleen,

kidneys, brain and myocardium. Grossly there was nothing remarkable in the heart except a polypoid tissue in the wall of the left auricle at the mouth of the pulmonary vein. This was firm and covered with intact endocardium, but consisted of a central core of cheesy material. Microscopically the myocardium had several tissue masses, histologically tuberculous. Acid-fast bacilli were not found in sections or by concentration methods.

Most instances of miliary tuberculosis of the myocardium were in subjects of the first decade of life. This may be due to the relatively larger tissue mass examined in the smaller hearts. Perhaps, if more microscopic preparations were made of the adult myocardium, the comparative rarity of miliary tuberculosis in adults would be less. Of course, the presence of miliary tubercles in young persons may be coincidental. There is another possibility: The hearts of youths with rheumatic fever and with subacute bacterial endocarditis frequently contain Aschoff nodules. This and the demonstration of tubercles in 9 per cent of the hearts of children in this series who died of generalized miliary tuberculosis may suggest that the heart in youth is more often the seat of the granulomatous lesions of rheumatic fever and tuberculosis. This, at present, cannot be linked with an immunologic phase peculiar or common to these diseases.

DISCUSSION

C. A. DELANEY: Did you attempt to demonstrate tuberculosis in the skeletal muscles of these patients with tuberculous myocarditis?

P. R. CANNON: I have been interested in the localization of bacteria in various organs following intravenous injection and have noted that most of the bacteria are removed by the liver, spleen and bone marrow in thirty minutes. The best explanation seems to be that the bacteria are not removed by other tissues because the endothelial cells in them are small, have little cytoplasm, and hence are not actively phagocytic.

L. E. DAY: Tuberculosis of skeletal muscle occurs rarely in cattle. In some of these muscle infections, the viscera, in the usual gross examination, have no tuberculosis. When the infection is deep in the muscles, the fascia is involved. Tuberculous myocarditis without lesions in other tissues has been noted in cattle.

HENRY HORN: Tuberculosis of the skeletal muscle seems to be less frequent than tuberculosis of the myocardium. The skeletal muscles in these patients were not examined.

Book Reviews

Parasitism and Disease. By Theobald Smith, Director Emeritus of the Department of Animal Pathology, Rockefeller Institute for Medical Research. A publication of the Louis Clark Vanuxem Foundation. Price, $2. Pp. 196. Princeton, N. J.: Princeton University Press, 1934.

Of recent and contemporary investigators of parasitism and infection, probably none has combined successful investigation with broad biologic interpretation in the same degree as the author of this book. This fortunate combination has established a leadership of wide influence. The book is the outcome of a desire on the part of the author "to bring together all alien invaders and parasites of the animal body and deal with them and the disturbance they produce under some unifying principle." That principle is the relation between parasitism and disease in its broadest manifestations, as determined in the main by the patient, comparative method of the naturalist. The struggle of living things to survive has established predacity and parasitism. Biologically, parasitism is a normal process, with pathologic manifestations in certain stages. In general, the relations between parasite and host are offensive and defensive, each parasite-host relation being more or less peculiar. This is the general theory that guides the presentation. In the large view, parasitism presents four phases, each with its own machinery: adjustment and adaptation to invasion, to multiplication, to emigration and to transfer to new hosts. Every successful parasite has solved its demands "in accordance with its capacities which it received from its free-living ancestors as matched against the resisting powers of the host." It is aberrant and incomplete parasitism that has greatest interest in the study of disease. "Aberrant movements are, on the whole, the most important factors in parasitism and in the diseases due to it. Aberrancy is the adventurous element in the life of the parasite, which leads either to death or to new conquests. Establishment in new hosts paves the way for the formation of new races and varieties, for the new host modifies and molds the invader until an equilibrium has been established. Aberrancy of parasites is furthermore responsible for much disease whenever they reach a more yielding host. This is almost the rule among protozoan forms. Most epidemics or pandemics are probably due to strayed parasites. A study of epizootics among small experimental animals kept together in large numbers tends to show that such diseases are most virulent at the start and gradually change their characters, becoming less infectious, more chronic, non-fatal and topographically altered as regards the incidence of lesions. The epidemic is probably the first sign of a straying of parasites from either near or more distantly related hosts or from an immune group to a susceptible group of the same species or race."

Medical science has been most concerned with the multiplication of the parasite within the host, that is, in the immediate host-parasite conflict. The attack on this stage in the parasitic cycle in order to save life and prevent infection has resulted in the great modern advances in the prevention and the treatment of infectious diseases. In the evolution of parasitism, offensive and defensive weapons develop on the part of both parasite and host. In the case of the host, this development is illustrated by the formation of specific antibodies and the development of phagocytic cells.

The last four chapters of this remarkable book deal with the variation and mutation among parasites, the survival of parasites and movement from host to host, epidemiology and the utilization of discoveries in parasitism. In these and in the other chapters the complex relations of parasitism to disease are discussed with great clearness and deep insight from a broad, biologic point of view. All forms of parasites receive attention—worms, protozoa, bacteria and invisible viruses. It is a stimulating book, which will interest a much wider circle than those interested merely in the medical or technical aspects of the subject. Two

more quotations may be permitted: "The final suppression [of epidemics] presupposes a world organization of human society without wars, and disarmed, such as the most pronounced idealist of today can scarcely conceive, but towards which human society must tend to survive in the struggle with animal and plant life, microscopic and ultramicroscopic" (page 168). . . . "The objectives of research as a mere accumulation of data or the display and parading of acquired knowledge in a world otherwise in motion is outmoded. Penetration into mysteries may thrill the penetrator and occasionally others, yet this is not enough. Discoveries and inventions must be made to yield some contribution towards that rather vague goal, the welfare of mankind. More specifically the study of parasitism and disease appeals to the human desire to live and be free from disease and it is this strong urge that furnishes ample stimulus to the altruist as well as to the charlatan. Parasitism is greatly favored by large numbers of individuals insofar as they offer the best opportunities for new parasites through trial and error methods to arise or for existing ones to develop a more complete adaptation. Large numbers of hosts furnish the starting points of epidemics and nature reduces the superabundance of wild life through disease. Nature may be said to abhor a crowd" (page 169).

Les ultravirus pathogènes saprophytes: techniques d'études, caractères physiques et biologiques, maladies à ultravirus, clinique, anatomie pathologique, epidémiologie, immunité. By Paul Hauduroy, Préparateur à la Faculté de Médecine de Paris. Price, 60 francs. Pp. 462. Paris: Masson & Cie.

An earlier book by the author on filtrable viruses ("Les ultravirus et les formes filtrantes des microbes") was published in 1929. Since then knowledge of so-called filtrable or ultramicroscopic viruses—the ultraviruses—has grown with amazing rapidity. In this book Hauduroy presents a comprehensive review of the present state of knowledge in this field. The first part of the book deals with the technic of filtration, ultrafiltration, cataphoresis, adsorption, cultural methods and staining. The second part is devoted to a description of the ultraviruses—saprophytic and pathogenic, of plants, bacteria, insects, birds and mammals. In the third and last part the principal characteristics of the ultraviruses are reviewed. Under the virus diseases in man are grouped smallpox and amaas, epidemic poliomyelitis, herpes, encephalitis, chorea, yellow fever, dengue, inguinal lymphogranulomatosis (inguinal granuloma is not discussed), influenza, coryza, warts, molluscum contagiosum, mumps, trachoma and measles. Rabies and vaccinia are described as primary in animals. In the section on sheep pox (*clavelée*) is an interesting citation from Pourquier (*Compt. rend. Acad. d. sc.* **101**:863, 1885; ibid. **104**:703, 1887), in which he described independently allergic phenomena in this disease that correspond exactly to the allergic phenomena described by Jenner, Boyce and others in smallpox and vaccinia more than one hundred years ago and by Pirquet in 1906. Pourquier's description is as follows: "If, during six successive days the same subject is inoculated with the same virus, the first four punctures only reach the stage of pustules, and in all development is complete and secretion is greatest from the fourteenth to the fifteenth day from the beginning of the experiment. There is consequently an inequality in the duration of the evolution, the first puncture showing secretion within fifteen days, the second at fourteen days, the third at thirteen days and the fourth at twelve days. This inequality in the duration of the evolution modifies the dimensions of the pustules, the diameters of which decrease. It appears from these observations that after the first twenty-four hours the first inoculation had already modified the soil (*terrain*). This influence is accentuated the following days, and immunity is acquired from the sixth to the seventh days: On the sixth day there is at least a papule, on the following days nothing. These differences in the evolution are due to a modification of the soil at the beginning of immunity."

Hauduroy's book gives an instructive and orderly account of what is now known about the ultraviruses. It will be of value to all who are interested in this new field of investigation.

Books Received

A Practical Treatise on Diseases of the Skin for the Use of Students and Practitioners. Oliver S. Ormsby, M.D., Clinical Professor and Chairman of the Department of Dermatology, Rush Medical College of the University of Chicago. With Revision of the Histopathology in this Edition by Clark Wylie Finnerud, B.S., M.D., Assistant Clinical Professor of Dermatology, Rush Medical College of the University of Chicago. Fourth edition. Cloth. Price, $11.50. Pp. 1288, with 622 illustrations. Philadelphia: Lea & Febiger, 1934.

Active Immunization Against Diphtheria: Its Effect on the Distribution of Antitoxic Immunity and Case and Carrier Infection. Sheldon F. Dudley, Percival M. May and Joseph A. O'Flynn with a note by J. Orr Ewing. Medical Research Council, Special Report Series, No. 195. Price, 3 s. Pp. 140. London: His Majesty's Stationery Office, 1934.

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